ARCHIVES OF SURGERY

VOLUME 37 SEPTEMBER 1938 NUMBER 3

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FANTOM LIMB PAIN

A REPORT OF TEN CASES IN WHICH IT WAS TREATED BY INJECTIONS OF PROCAINE HYDROCHLORIDE NEAR THE THORACIC SYMPATHETIC GANGLIONS

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After the amputation of an extremity it is usual for the patient to have sensations that are ascribed to the absent limb. In the majority of cases these sensations are most vivid immediately after the amputation and as time passes tend gradually to fade from consciousness. Not infrequently, however, the absent limb becomes the apparent site of such severe symptoms that the patient not only becomes more keenly aware of the fantom limb than of his normal extremities but may be so distracted by the unbearable quality of his pain that he loses his social usefulness.

The attention of the surgeon who undertakes to relieve pain in the fantom limb is naturally concentrated on the nerves in the stump, not only because they are the conveyors of painful sensation but because they represent the only type of tissue at the site of amputation that continues to grow. The skin, the muscle, the fascia and the bone tend toward atrophy rather than toward continued growth, but the individual nerve fibers continue their blind effort to grow down into the absent limb. Meeting with resistance, they snarl up into a twisted mass, which if large enough to be palpated is called a neuroma. Various methods of treatment of the cut ends of nerves have been advocated to prevent the formation of neuromas, but it is probable that some degree of piling up of nerve fibers in the scar tissue takes place at the cut ends of all nerves, no matter what method of treatment is used. Such a neuroma may or may not become hypersensitive. A definite neuroma which on palpation causes a shocklike sensation flashing out into the fantom limb over a known nerve distribution can sometimes be treated successfully by local excision and injection of alcohol into the cut end of the nerve.

But pain in the fantom limb, described in the case histories which follow, is decidedly different from the pain caused by a hypersensitive neuroma. The condition may exist in the absence of palpable neuromas. The stump may seem faultlessly constructed. Usually the stump is

cold; sometimes it is clammy with sweat, and occasionally it is discolored and edematous. None of these characteristics, however, appears to be essential to the condition, since the pain may occur in the absence of any of these objective findings. Perhaps the local coldness of the stump is the most constant objective finding, although I have observed 1 case (case 8) in which the attacks of pain were associated with actual increase in the temperature of the stump and dilatation of the veins. In most cases there are vasomotor and sudomotor disturbances in the stump. The most constant and annoying symptom of which the patient complains is a sensation of "tension." One sufferer gave a most impressive illustration of this sensation. He asked me to clench my fingers tightly over my thumb, strongly flex my wrist and then raise my arm behind my back in the "hammer-lock" position. I was told to hold this posture. At the end of three minutes the discomfort in my hand and arm had grown unbearable, and I was perspiring freely. I took my arm down and relaxed my stiffened fingers. "Yes," he remarked, "but *you* can take your arm down."

As Leriche [1] has pointed out, the pain seems to be out of all proportion to any objective findings in the stump, so that to the observer it may appear to be grossly exaggerated. The bizarre symptoms ascribed to an extremity that is no longer present, the inexplicable variations in their intensity and the fact that the subject may be diverted at times so as temporarily to forget his pain all suggest that the pain is "central" and hence not amenable to surgical treatment. Such a conclusion seems to be borne out by the concomitant signs of nervousness, excessive sweating, exaggerated reflexes and emotional instability that frequently are associated with the syndrome of fantom limb pain.

In this paper I shall not enter into a discussion of this explanation of the pain picture, except to concede that a protracted period of suffering from any cause will profoundly affect a patient's ability to tolerate pain. In such a state of hypersensitiveness the patient may interpret as painful a number of afferent impulses which ordinarily are below the pain threshold. But my observations of patients with pain in the fantom limb do not allow me to escape the conviction that there is a physical basis for the original pain phenomena. Just what that physical basis may be is still obscure, but that it exists I cannot doubt. In my capacity as medical examiner for the state industrial accident commission of Oregon I have had the opportunity to examine a considerable number of men who have had amputations of an upper extremity. The proportion of these who feel pain in the fantom limb is surprisingly high, and the similarity in their complaints is so striking as to warrant the term "fantom limb pain *syndrome*."

1. Leriche, R.: Les douleurs des moignons d'amputation, Presse méd. **40**: 869-873, 1932.

Ten cases have been selected for report in this paper. In all of these the patients have had one or more injections of procaine hydrochloride near the thoracic sympathetic ganglions of the affected side. In 8 of the cases the patient felt immediate relief from pain, together with an extraordinary sequence of subjective and objective changes. In 4 of these 8 cases the relief was of sufficient degree and duration to suggest that injection of procaine hydrochloride is of therapeutic value in such cases. However, the purpose of this paper is not to advocate any particular method of treatment but rather to call attention to the pain syndrome by the presentation of actual cases and to discuss briefly the implications of the observations here recorded in relation to the general problem of pain.

REPORT OF CASES

CASE 1.—C. W., a man aged 54, lost his right hand on July 15, 1929. His hand was jerked into a sprocket wheel, from which it could not be extricated for several minutes. A few hours later the mangled hand and forearm were amputated about 2 inches (5 cm.) below the elbow. He did not suffer any unexpected amount of pain during the month required for the healing of the surgical wound. When he left the hospital, at the end of six weeks, he was conscious of a "deep, heavy pain" in the top of the right shoulder. In the next few weeks this pain became gradually eased, but in the same interval he became increasingly aware of the absent hand. It felt as if it were in a cupped position, tipped slightly toward the ulnar side. He was not able to move any of the fingers. At times he would feel "cramps" in a finger or in the whole hand associated with a "smarting, tingling sensation." When the stump was exposed to cool air the forearm would feel "icy cold." This sensation rarely involved the fantom hand, which was more commonly the seat of a burning sense of heat, "as if it were held too close to a hot stove." He complained of "shooting pains" in various parts of the hand, but his chief complaint was of a sense of "terrible" tension, "as if the muscles were set and the skin too tight." When this sensation was most intense the sweat would pour from the axilla so as to soak his shirt and sleeve. In times of emotional excitement he could be diverted so as to forget his pain momentarily, but there was a peculiarly unbearable quality in it that prevented him from reading or doing any sedentary task. Although the pain was described as being worse during the day, his sleep was fitful and he stated that he was "worn out" with pain.

The stump was well constructed and of normal color. It was cold to palpation and extremely hyperesthetic. He seemed to tolerate light touch less well than a firm grasp of the stump. At each end of a curved scar across the cubital fossa was a definitely localized point of special tenderness which had been called a neuroma. Similar neuromas had been excised previously from other areas, without relieving the pain. When these sensitive spots were touched the patient would jerk away and complain of a shocklike pain which required several minutes to subside. He constantly guarded the stump with his other hand and was of the impression that this guarding continued even during his sleep. Motion at the shoulder and elbow was restricted, and the muscles were weak. When one flexed the elbow sharply there was precipitated a clonic jerking of the stump which he could not control. There was a tendency for the jerking to come on spontaneously. He was seen to rub the stump gently with his other hand at times. He explained

that rubbing the stump seemed to alter the character of the pain in some fashion, but he was not sure that it was diminished materially by the action.

When a sphygmomanometer cuff on the upper part of the arm was inflated just sufficiently to cut off the arterial circulation, he reported a definite relief from the pain. One could then touch the "neuromas" without eliciting the shock-like pain. In addition, he reported that the feeling of tension in the fantom hand was distinctly less. When the pressure was released the stump flushed normally, and the sensitiveness returned within a few seconds.

On Jan. 14, 1931, 8 cc. of a 1 per cent solution of procaine hydrochloride was injected in the region of the stellate and the second dorsal sympathetic ganglion on the right side. Horner's syndrome (slight) was noted, and the temperature of the stump rose several degrees. With the rise in temperature he reported a subjective sense of warmth and relaxation in the absent limb, which he said was most pleasant. He felt that he could move his fingers one after the other. The neuromas in the stump could no longer be located by the patient. He could flex his elbow without precipitating the clonic jerking. The fantom hand felt comfortable and relaxed for several hours after the injection. There was some return of the feeling of tension the next morning, but during the two succeeding days, in which he remained under observation in the hospital, the discomfort, tension and jerking, as well as the local hyperesthesia of the stump, were much less than before the injection. On the basis of the degree of temporary relief afforded by the procaine hydrochloride I advised a sympathectomy, but because of the uncertainty of the final results the operation was not authorized. At that time I had no reason for thinking that the temporary benefit might persist, and my attention was focused on the interesting observation of the disappearance of the neuromas during the test. I have been unable to trace this patient and cannot state whether or not his pain recurred in its original severity.

Case 2.—X, a physician aged 41, sustained a puncture wound of his left hand in 1926, when a glass syringe containing Bacillus welchii broke as he was injecting the bacillus into a guinea pig. Virulent and rapidly spreading gas gangrene made its appearance in the arm during the night, and on the following morning the arm was amputated about 2 inches (5 cm.) below the shoulder. For several days the wound bubbled gas and drained quantities of serous material. He felt pain in the fantom hand from the first day after the amputation. There was a sensation that came and went in the thenar eminence as if a sharp scalpel were being repeatedly driven into the flesh. The fingers seemed to be tightly clenched over the thumb, and he could not relax them. At times the whole arm felt as if it were held in rigid extension. After exposure to cold the tension increased, particularly in the thumb and in the first two fingers. When the sensation reached a certain intensity he felt a "boring" pain that began in the tip of the index finger, ascended the hand to the wrist and then spread in a diffuse manner over the entire fantom limb. The pain required about thirty seconds to reach the shoulder, at which time the muscles of the shoulder girdle began a series of rapid jerking contractions which he was unable to control. When the pain was at its height he became pale and was nauseated. As the pain faded, the sense of tension in the fingers was diminished, but never to a degree sufficient to permit them to be moved. In the intervals between the sharper attacks of pain he felt a persistent "burning" in the hand. The pain was not unbearable, and at times he could be diverted so as to forget it for a short interval. When it became annoying a hot towel thrown over the shoulder or a drink of whisky gave him partial relief.

On June 28, 1932, during a particularly severe bout of pain, an injection of procaine hydrochloride solution was given near the cervicothoracic sympathetic ganglions on the left side. Horner's syndrome was present. He reported that the individual fingers of the fantom hand began to feel warm and to relax, and for the first time in years he felt that he could move the fingers. He could not precipitate pain by moving the stump, slapping it or doing any of the maneuvers that had previously brought on an attack. When the effect of the procaine hydrochloride wore off the pain did not recur to the degree in which it had been present before the injection, and he enjoyed a considerable amount of relief for six months.

More than a year after the first injection this patient returned, complaining of severe pain which he said was of a different type from that which had been felt previously. He had never had a recurrence of the "boring" pain, and the clonic contractions of the stump no longer bothered him. For several months, however, he had been aware of increasing tension in the fantom hand and an intolerable feeling of constriction around the shoulder girdle. He had been on a hunting trip in Canada about a month before I saw him. The weather had been chilly, and although he wore a woolen sock over the stump it had become cold. He believed that the exposure had aggravated his distress. The stump was extremely cold, having a temperature 10 or 12 degrees (F.) lower than that of the trunk. His shirt was constantly wet with perspiration for its whole length on the side of the amputation. On Oct. 12, 1934, 5 cc. of a 2 per cent solution of procaine hydrochloride was injected near each of the upper four thoracic sympathetic ganglions on the left side. When the second needle was inserted below the second rib he complained of a sharp, stabbing pain in the base of the thumb. This fantom thumb was felt to be tightly compressed within the palm by the clenched fingers. An hour after the injection all of the digits except the thumb felt warm and relaxed. The thumb remained pressed into the palm, and a few hours later he noticed an intense sense of burning in this digit, which soon spread to involve the hand and arm. The pain lasted all night, so that he slept less than two hours in spite of the use of a hypnotic. The next day the burning sensation gradually disappeared, and that night he slept soundly for nine hours. In the three years that have elapsed since this second injection there has never been a return of his original pain. The stump has remained warm and less sensitive, there is no jerking of the muscles, and he considers himself "cured."

CASE 3.—R. H. D., a man aged 54, lost his right hand on Oct. 31, 1933. He was employed in a shingle mill and became caught in a saw which severed the right forearm in its middle third and slashed a great wound in his chest and abdomen. At the end of nine weeks his wounds were completely healed, but there was restriction in the range of motion at the shoulder. He also began to complain of pain and sensitiveness in the stump and of increasing tension in the fantom hand. The arm and shoulder muscles began a convulsive jerking which was annoying and uncontrollable. This was associated with "cramping" in the fingers. He said it felt as if there were a wire down the center of his arm to which his fingers were attached. He also spoke of feeling as though some force were pulling on the wire "as if to pull the fingers up through the arm." At times the hand felt hot, as if held by force too close to a hot stove, and the fingers became the seat of intolerable burning. He could not move the fingers voluntarily, but they tended to shift their position over one another, and in so doing would "get caught in cramps." The thumb was apt to abduct and then slowly draw down over the fingers with great force; then the wrist would slowly flex strongly, and the whole hand and wrist would ache. Interspersed between the muscular

contractions he felt knifelike stabs of pain through the hand and fingers. When the burning sensation was absent the general feeling of the hand and wrist was one of coldness, although this was seldom of an unpleasant degree.

As the patient's symptoms progressed he was noted to have a rapid pulse, to tremble all over and to sweat profusely while talking to the examiner. His physical and mental attitude showed a shrinking away from all contacts, and he was incapable of carrying out the simplest transactions. He could not read for any length of time, and his sleep was disturbed. Hyperesthesia of the stump prevented him from wearing his artificial limb. The jerking of his muscles, his mental attitude and what was considered an exaggerated hyperesthesia of the stump led to his being classed as a patient with "hysteria." He repeatedly refused to consider a closure of his claim against the state industrial accident commission, claiming that his pain prevented him from ever doing any work again. A long course of physical therapy, excision of numerous "neuromas," correction of dental sepsis and psychotherapy failed to bring about the slightest improvement in his condition.

In June 1935 a 2 per cent solution of procaine hydrochloride was injected near the third, fourth and fifth thoracic sympathetic ganglions on the affected side. A small amount of iodized poppyseed oil was injected through each needle before it was withdrawn, and subsequent roentgenograms showed the material deposited along the sides of the vertebral bodies near the ribs from the third to the sixth. There was no Horner syndrome, but there was a prompt subjective sense of warmth and relaxation in the fingers of the fantom hand. The thumb slowly moved outward from the fist position, and one by one the fingers opened. The stabbing pains and the jerking of the stump ceased. The two neuromas which had been marked out on the stump before the injection were no longer sensitive.

Examined in November, the patient was found to be wearing his artificial limb continuously. He said he occasionally felt sensations of cold or transient pains in the fantom hand and that at rare intervals the shoulder muscles would jerk, but he expressed himself as delighted with the improvement in his condition. The hyperesthesia of the stump was gone; he slept soundly at night; he had gained in weight, and the change in his physical and mental attitude was apparent in his demeanor and in his request for closure of his claim.

Case 4.—R. A. H., a man aged 45, lost his left arm in a railroad accident on April 26, 1934. While working as a brakeman he fell with his elbow across the rail; a train wheel passed over the upper part of the arm and the forearm. He sustained multiple fractures of the ribs, shattering of the pelvis, rupture of a kidney and dislocation of a hip. The partial amputation was completed in the hospital within five hours of his accident. He remembered little of what went on around him for the first four weeks. In June he began to notice an increasingly painful tension in the fantom hand, which soon obscured all his other discomforts. The hand felt as if it were tightly clenched, and in cold weather it would ache as if it had been struck a hard blow. When the pain was severe he could not rest. He could always tell when he was about to fall asleep because the fingers would seem to relax slightly, and the hand would drop forward at the wrist. Later, the forearm became painful, "as if it had been scratched and skinned from the elbow to the wrist." The fantom hand seemed smaller than the remaining hand, and the arm seemed short. The arm felt as it were in a position of elbow flexion, but he thought that if it were hung straight down it would reach about to his waist. The stump was so hyperesthetic that he could not permit its being washed; it had become foully dirty and was covered with flakes of dead skin. He could not lie in any position which put strain on the involved shoulder. A patch of skin in

the cubital fossa was said to itch severely. He was unable to move his fingers from the fist position. At times the fingers would press harder into the palms, the nails would feel as if they were pressed inward "toward the bones," the wrist would flex and the pain would become "dreadful." During the three months before he was given an injection of procaine hydrochloride he slept only under the influence of hypnotics, and the fitful sleep did not rest him. He trembled and perspired freely. He cried when attempting to carry on a conversation, and he talked frequently of suicide.

In September 1935 procaine hydrochloride was injected near the thoracic sympathetic ganglions on the left side from the second to the fifth. Severe pain promptly developed in the precordial region. He became extremely pale; his respirations were shallow, and his pulse was rapid and weak. Although this alarming reaction lasted but a few minutes, he continued to complain of pain in the left side of the chest for about three weeks. This pain occupied his attention, but he reported a sense of warmth and relaxation in the fantom arm. He felt that he could move all the fingers except the index finger.

This man was examined at frequent intervals in the year and a half following the injection. His multiple injuries combined to produce permanent total disability. His syndrome of fantom limb pain, however, remained alleviated. The stump stayed warm and dry and lost its hyperesthesia, so that it could be kept clean and soft. There was no longer need to guard the shoulder. He said that he would gladly submit to another injection and accept the risk of another complication in the chest similar to that following the previous injection, but no further injections have been required.

CASE 5.—C. H., a man aged 60, had his right arm partially avulsed at the shoulder when it became caught in a gear in November 1931. The amputation was completed within a few hours, and a large denuded area in the axilla was partially covered with grafts of skin from the abdomen. He was not particularly conscious of the fantom hand during the first six weeks after the amputation. He then began to have three different types of pain ascribed to the absent limb. The first sensation was a continuous burning heat, "like fire in the fingers and hand." The index finger was least affected; the thumb and remaining three fingers were most affected. The second sensation was that of "tightness" associated with a sense of "trembling, drawing and twisting" in the hand and arm. The third type of pain was intermittent and was described as "shooting stabs of pain" throughout the limb. These pains were variable in intensity, but he claimed never to have been free from them for more than twenty minutes during his waking hours. He did not think that his sleep was seriously disturbed and stated that the arm "goes off to sleep two or three times before I can get to sleep." He wore a steel-reenforced leather shield over the shoulder to protect it from any contact, the scar being so sensitive that blowing one's breath across it caused him to cringe and the shoulder muscles to jerk.

At the time of the injection in October 1935 the fantom hand was described as being in a clawlike position, which he could not alter except by moving the index finger slightly. This patient knew that some sort of test was to be performed on his back, but I had purposely refrained from explaining the procedure or telling him what he might expect from it. Procaine hydrochloride was injected near the thoracic sympathetic ganglions from the third to the sixth, and he was asked to report any changes in sensation. He promptly reported that the hand was becoming warm and that he could move all of his fingers. There

was a pleasant sense of relaxation, and the "twisting" tension disappeared. The scar was no longer hyperesthetic, and the jerking of the muscles subsided. In the next few days the fantom hand, which had always felt somewhat smaller than normal, seemed to shrink still more, so that the arm felt to be about 6 inches (15 cm.) long and the hand "about as big as a dollar." Examined three months after the injection, he reported a satisfactory degree of relief, but fourteen months later he returned, complaining of a recurrence of the original pain. On the day he was brought to me by his local physician he had a sharp stab of pain, so severe that he fell to the floor in a faint. On Dec. 14, 1936, a 2 per cent solution of procaine hydrochloride was injected near the third to the seventh thoracic sympathetic ganglion and was followed by the injection of a small amount of dilute solution of quinine and ethyl carbamate (urethane). He again reported a prompt relief from pain and tension, but by March 1937 the fingers no longer felt movable, although the pain had not recurred. The dorsum of the hand was said to feel colder than the palm. In May he reported that the pain had come back. A thoracic ganglionectomy was performed by the posterior approach, the fourth and fifth sympathetic ganglions being excised and the proximal end of the chain being buried in intercostal muscle. Again there was relief from the pain, but within a month it had begun to come back. In August I injected procaine hydrochloride near the stellate ganglion, without appreciably altering his subjective complaints, and later in the same month I divided the brachial plexus high in his neck. The nerve trunks were divided close to the vertebral foramens, alcohol was injected, and the cut ends were closed with fine silk sutures. I regret that I cannot say definitely whether or not the division of the nerve trunks was proximal or distal to the point at which the gray rami join them. The nerve trunks at the point of section were not involved in scar tissue and appeared normal in cross section. Instead of relieving his pain, the operation made it worse. He said that the hand was as tense as ever and the pain unbearable. He entered the hospital in December 1937 prepared for a chordotomy, but he wished me to try more injections of procaine hydrochloride first. An infiltration of the first, second and third thoracic ganglions with 2 per cent solution of procaine hydrochloride relaxed and warmed the hand. The pain was again completely relieved, but at this writing an insufficient interval has elapsed to permit decision as to whether or not repeated injections will help him permanently.

Case 6.—J. C., a man aged 40, had his left hand severed at the wrist by a wood saw in September 1931. Infection developed in the stump, and multiple incisions were made in the forearm. Healing was complete in two months, during which interval he felt considerable pain in the stump but was not particularly aware of the fantom hand. With the clearing of the local infection, however, his pain seemed to center in the hand. It felt as if it were in a rigid cupped position. He complained of severe burning, most intense in the index finger and thumb. At times the index finger seemed to begin jerking and the whole arm gradually became involved in an uncontrollable twitching. He complained of an ache in the shoulder which spread down the arm to the hand, after which sharp stabbing pains occurred in the fingers. In the interval between September 1931 and July 1935 he had four operations on the stump, three for neuromas and one for the excision of scar tissue and a small exostosis on the end of the radius. None of these operations gave him relief. The stump was cold and clammy, and there were slight edema and cyanosis at its end. The skin could be moved freely over the bones, but subjectively this part of the skin felt as if it were drawn over the ends of the bones like tight parchment.

In July 1935 procaine hydrochloride solution was injected near the second to the seventh thoracic sympathetic ganglion. There followed a prompt relief from pain and tension in the fantom hand and in the stump. He felt that he could move the fingers for the first time since the accident, and, although the hand had not felt particularly cold previously, it was now agreeably warm. Examined in January 1936, he stated that the fingers had gone back to their cupped position. He could no longer move them but stated that the tension was not great. He had not obtained complete relief from pain in the fantom hand but said that the remaining pains were bearable. The stump no longer felt tight, and he could tolerate wearing his artificial arm, which he had been previously unable to wear. He had secured a job and wished to continue with it, promising to return for further injections should they be needed.

CASE 7.—G. M., a man aged 43, in October 1934 had his left hand and forearm caught in some gears, which "chewed up" the tissues so completely that amputation just below the elbow was necessary. He complained of occasional cramping in his fingers, which seemed to be maintained in a tightly clenched posture, but his chief complaints related to the stump. It was cold much of the time but at times would become flushed and hot, sometimes showing "welts." It was usually of a cyanotic color. He had had neuromas removed three times, and the stump had been remodeled twice. In May 1935 the ulnar nerve had been resected 3 inches (7.5 cm.) above the elbow, and alcohol had been injected into its proximal end. These operations had afforded little, if any, relief. In January 1936 procaine hydrochloride was injected near the second to the sixth thoracic sympathetic ganglion. Beyond a slight warming of the stump there were neither subjective nor objective evidences of improvement. He was then given a long series of treatments by alternating pressure in a pavaex unit, which afforded more temporary relief than any treatment previously given.

On December 7 and 8 he was given injections of procaine hydrochloride solution. The first injection was in the region extending from the level of the third to that of the seventh thoracic ganglion, and the one on the following day was in the region of the first to the fourth ganglion. No appreciable benefit was conferred by either injection. In the latter part of the same month his arm was reamputated through the middle third of the upper part of the arm, and an effort was made to conserve for skin flaps only areas of skin that had been least cold and discolored. He noticed immediate relief after this operation. Examined in November 1937, the stump was again cold and cyanotic. It was becoming increasingly hyperesthetic, and he was aware of a feeling of increasing tension in the fantom hand. He insisted that his condition was still better than it had been before the reamputation, but there was evidence suggesting that his original symptoms were returning.

CASE 8 (courtesy of Dr. Howard Naffziger).—L. A. P., a man aged 51, "wrenched" his left shoulder in climbing a trestle in September 1930. A month later he began to notice numbness and tingling in the fingers, and the hand gradually assumed a cadaveric appearance. In November the index finger and the distal joint of the thumb were amputated for spreading gangrene. The wounds failed to heal. Conservative treatment was unavailing, and in January the hand was amputated above the wrist. The stump healed by primary intention within ten days, but the agonizing pain that had been present before the amputation recurred within two days of the operation and remained constant. In March 1932 a "sympathectomy" was done, but the report does not make clear exactly what procedure was carried out, and when I examined the patient in February 1936 there was no evidence of a vasomotor change in the stump, and Horner's

syndrome was not present. In May 1932 a periarterial sympathectomy was done on the brachial artery, and in September of the same year a muscle was divided in the cervical region. None of these operations conferred any lasting benefit.

The patient complained of recurrent series of sharp pains in the fantom hand. It seemed to be tightly clenched, and he was unable to open it. The pains were aggravated when he felt nervous and were partly relieved by bromides. They were definitely worse when the stump was warm, and for the preceding three years he had been subject to periodic attacks in which the veins of the forearm would become distended and the stump more red and hot than usual. At such times the pains were invariably worse. There was no extreme hyperesthesia of the stump, but he was unable to tolerate for long the wearing of an artificial limb. The peripheral arteries were no longer palpable. No increase in sweating had been observed.

In February 1936 solution of procaine hydrochloride was injected near the upper thoracic sympathetic ganglions, without producing appreciable subjective or objective changes.

Case 9.—A. A. P., a man aged 52, had his left arm crushed between his automobile and a street car in February 1933. When he recovered consciousness after the accident his arm had already been amputated close to the shoulder. He complained of "terrific" pain in the fantom limb present "from the very first minute." In addition to a constant and intolerable feeling of tension, the fingers felt as if the flesh were being torn from around the nails. The wrist felt as if a tourniquet or a wire were tightly constricting it. The arm seemed to be flexed at the elbow, with the forearm extended from the body and the fingers in a cupped position. At intervals this posture changed involuntarily to the extended position of the elbow, and then the fingers would clench tightly into the palm. Although he could not alter the position voluntarily, the hand would occasionally "get to going," the fingers would slide over one another and twist and the hand would "jerk." The jerking would always extend to involve the stump, and he was in the habit of grasping it tightly to prevent its "flapping about." Even when the stump was tightly held the jerking of the muscles would persist. The hand felt "constantly cold and damp," "as if it were in cold water." The pain in the hand was aggravated by taking cold food or drink and also by cold weather. In June a dorsal sympathectomy was performed. The patient was left with a Horner syndrome, but there was no relief from pain and the sweating persisted. He stated that the left side of his body sweat more than the right and that this involved the entire side rather than only the axillary region. In the fall of 1933 an operation on the brachial plexus failed to give him any relief. He had become dependent on large doses of dilaudid hydrochloride supplemented by phenobarbital sodium and sodium amytal for the relief of pain and to permit him to sleep. At the time I examined him, in August 1936, he was using more than a grain of dilaudid hydrochloride daily.

The stump was soft and warm. There were a few sensitive spots in it, but no definite neuromas and no excessive hyperesthesia. When one stroked downward along the stump he complained that it caused an unbearable pressure to be transmitted into the hand. On Aug. 24, 1936, procaine hydrochloride was injected in the region extending from the level of the third to that of the seventh thoracic ganglion. There was an immediate subjective sense of relaxation in the hand, but no feeling of warmth was present. In the ensuing week he described a variety of new experiences and sensations in the fantom limb, all of them interpreted by

him as indicative of improvement. There was no jerking of the muscles, and the stump was slightly warmer to palpation. The arm had changed to the extended position, but the fingers were not clenched. Downward stroking of the stump did not cause discomfort.

On October 1 the injection was repeated, since he still complained of pain in the hand. This time he reported a definite subjective warming of the hand, increased freedom of motion at the shoulder and still more reduction in the pain. He said that his left upper eyelid felt "less heavy" and he thought that it drooped less. I was unable, however, to confirm this impression. A few weeks later he said that he was greatly relieved of pain and was rapidly ridding himself of his dependence on opiates. However, subsequent indirect reports indicated that he continued his addiction and, after an automobile accident in which he was shown to be at fault, had been committed to a state hospital. I have not been able to secure an accurate report of his condition as regards pain in the fantom arm.

CASE 10.—E. C. P., a man aged 50, crushed his hand and forearm in some carding rolls in October 1934. The crushed tissues became infected, and after three months of draining, during which time the patient complained of terrible pain in the hand and fingers, an amputation was done just below the elbow. The operation did not relieve the pain, and for a time he insisted that the fingers were still on. He complained of pain under the finger nails, across the knuckles and in the palm of the hand. There was a constant ache in these parts, which was aggravated when he smoked cigarets, "as if the fingers swelled more." The stump was sensitive to both deep and superficial contact, and the skin covering it felt extremely "tight." He suffered from sudden shocklike pains which came on "like the kick of a mule" at irregular intervals of the day or night, sometimes as often as twenty-four times in one day. The fantom hand was described as being in pronation, with the fingers fixed in a clawlike position and the thumb extended. He believed that he could move his wrist slightly but said he could not move his fingers. He made attempts to clench the hand into a fist, feeling that movement of the fingers might ease the pain. At odd times the stump might jerk suddenly, but he had no clonic contractions and no twitching of the muscles. The stump was well constructed, and the tissues were soft. The skin was of normal color but was colder than normal. I was unable to get a blood pressure reading from the upper part of the arm. When the cuff pressure was maintained above 120 mm. of mercury (the systolic pressure for the normal arm) he reported a feeling of relaxation in the hand and in the stump. The stump might then be palpated without causing him distress. No definite neuromas were found.

In January 1936 solution of procaine hydrochloride was injected near the third to the eighth thoracic sympathetic ganglion on the left side. He became pale, and his blood pressure dropped so that it could not be recorded. He was nauseated and wet with perspiration. The heart action was slow and the sounds distant for more than an hour. For several days after the injection he complained of pain in the left side of the chest "around the heart." During the same interval he felt a distinct warming and relaxation of the fantom hand. The stump was warm and had lost its hyperesthesia. There was a definite increase in the range of motion at the shoulder. The relief afforded by the injection remained satisfactory for about three months. His wife then wrote me that the pain seemed to be coming back, but up to the present time (January 1938) he has not returned for further injections.

COMMENT

On reviewing the literature I find that the method of treating fantom limb pain by infiltration of the sympathetic ganglions with procaine hydrochloride is not new. In an article dealing with repeated injections in the region of the stellate ganglion for a variety of painful conditions, Leriche and Fontaine [2] stated that patients with neuralgia in the amputation stump have been relieved of pain by this method. In the brief paragraph given this subject they made two interesting observations: first, that the method has proved so successful as a means of treatment that they have abandoned all surgical operations on such patients; second, that they have found it of distinct advantage also to inject the solution near the second thoracic ganglion. In fact, they concluded that better results can be obtained by giving the injection in the region of the second thoracic ganglion alone than by injecting the solution near the stellate ganglion.

Until recently most surgeons in treating vasomotor syndromes affecting the upper extremity directed their attack on the stellate ganglion. This ganglion was selected as the focal point because in it were supposed to lie the postganglionic cells of the vasomotor nerves to the arm and hand. Presumably, all impulses originating in the preganglionic cells in the midthoracic portion of the spinal cord must pass through this ganglion to reach the brachial plexus. My own early operations on the sympathetic pathways of the upper limb were directed at the stellate ganglion, but in June 1931 [3a] I operated on a patient in whom dense adhesions between the pleura and the vertebral bodies in the region of the stellate ganglion blocked my dissection and led to the removal of the third thoracic ganglion only. The immediate result was so satisfactory that in the following month [3b] I deliberately confined my operation to the third thoracic ganglion.[3] Since that time I have come to believe that a sympathectomy at the level of the third thoracic ganglion gives results superior to those obtained by an excision of the stellate ganglion. Not only does the operation at a lower level prevent the appearance of Horner's syndrome and leave intact important pathways from the spinal cord to the head and the thoracic viscera, but the end results seem to be better in that there is a more nearly complete relief of symptoms and recurrences are fewer. Smithwick [4] and Telford,[5] independently, have come to the same conclusion.

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2. Leriche, R., and Fontaine, R.: L'anésthesie isolée du ganglion, étoilé, Presse méd. **42**:849-850, 1934.

3. Livingston, W. K.: The Clinical Aspects of Visceral Neurology, Springfield, Ill., Charles C. Thomas, Publisher, 1935, (*a*) p. 145; (*b*) p. 101.

4. Smithwick, R. H.: Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity, Ann. Surg. **104**:339-350, 1936.

5. Telford, E. D.: Technique of Sympathectomy, Brit. J. Surg. **23**:448-450, 1935.

Different explanations have been offered as to why the operation at a lower level gives better results. Kuntz [6] called attention to the relatively constant bundle of fibers connecting the second thoracic ganglion with the brachial plexus and suggested that sympathetic fibers from still lower levels may ascend in the vertebral canal to join the lower nerves of the brachial plexus by way of the corresponding intervertebral foramens. In view of this contribution it appears that functioning sympathetic fiber tracts may be left intact when the operation or injection is confined to the region of the stellate and the second thoracic ganglion. White [7] and Smithwick [4] considered the operation on the stellate ganglion to be essentially a "postganglionectomy" and the operation at a lower level to be a "preganglionic section," and they interpreted the better results following the latter operation as due to the fact that after postganglionic fibers degenerate the blood vessels become hypersensitive to the action of circulating epinephrine and the sensitivity following preganglionic section is considerably less. Personally, I have come to feel that the hypersensitization to epinephrine observed in experimental animals after postganglionic section has been overemphasized in attempts to explain the unsatisfactory results of cervicothoracic sympathectomy in the treatment of human beings with vasomotor disturbances. It has never been proved that there is not in the third thoracic ganglion (or even lower) in human beings an important component of postganglionic cells related to the upper extremity. I have felt that some such possibility as this may account for the better results obtained by operations below the second thoracic level as compared with the results of those centering in the region of the stellate ganglion. At least, in my experience, injections of procaine hydrochloride in the region extending from the second to the level of the sixth or seventh thoracic ganglion by a technic modified from the method of Labat [8] have given more complete and lasting results than injections in the region of the stellate ganglion.

In some of the cases of fantom limb pain here reported, the beneficial effects of the injection have persisted for weeks or months. These are not isolated observations confined to cases of fantom limb pain. Flothow [9] and White [7] have reported cases of painful syndromes in which a single diagnostic injection of procaine hydrochloride afforded

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6. Kuntz, A.: The Autonomic Nervous System, J. A. M. A. **106**:345-350 (Feb. 1) 1936; The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929.

7. White, J. C.: The Autonomic Nervous System, New York, The Macmillan Company, 1935.

8. Labat, G.: Regional Anesthesia, Philadelphia, W. B. Saunders Company, 1930.

9. Flothow, P. G.: Injections of the Sympathetic Nervous System, California & West. Med. **44**:182-186, 1936.

lasting relief. This persistent benefit is difficult to explain because under ordinary circumstances after local infiltration or regional blocking of a peripheral nerve the anesthetic action disappears within a few hours. One may assume that the injection of the drug directly into the ganglions destroys some of the nerve cells, as it is well known that the toxic action of procaine hydrochloride is greater when it acts on nerve cells than when it acts on nerve fibers. This assumption seems to be supported by the observation that persistence of the increase in surface temperature of the stump and a lasting reduction in the amount of sweating may accompany the relief of pain. However, it is not necessary to make such an assumption, because procaine hydrochloride acting only on nerve fibers may also result in a lasting relief of pain. Infiltration with procaine hydrochloride around painful joints, into muscle, around major blood vessels or in sensitive scars often is followed by an interval of complete cessation of pain long after the anesthetic effect has disappeared. If the pain recurs, the next injection may bring about a still longer interval of relief, and repeated injections may afford a "cure." This is true particularly in the obscure types of pain associated with phenomena indicating that the sympathetic nerves are overactive. For the past few years I have been using this method of treatment, with a considerable degree of success, in cases in which long-continued, atypical pain in the extremities followed traumatic lesions. It is difficult to see why the relief from pain should persist in some cases and not in others, but I am inclined to think that the procaine hydrochloride temporarily interrupts a vicious circle of reflexes, which does not at once reestablish itself. This possibility will be referred to subsequently.

When injections of procaine hydrochloride near the second to the seventh thoracic sympathetic ganglion are successful in relieving fantom limb pain the sequence of objective and subjective changes that ensues is little short of miraculous to the patient and the observer alike. The pain disappears; an increasing sense of warmth and relaxation pervades the cramped extremity, and one by one the fingers open and can be moved voluntarily. The relief of pain, with its associated peripheral vasodilatation, is so consistent that one cannot escape the conclusion that impulses conveyed by the sympathetic nerves, either efferent or afferent, must have been contributing to the painful phenomena.

It would not be difficult to explain the relief of pain if it were known definitely that the sympathetic pathways transmit painful sensation from the arm. A few careful observers, such as Foerster,[10] Reschke[11] and

10. Foerster, O.; Altenburger, H., and Kroll, F. W.: Ueber die Beziehungen des vegetativen Nervensystems zur Sensibilität, Ztschr. f. d. ges. Neurol. u. Psychiat. **121**:139-185, 1929. Foerster, O.: Ueber das Phantomglied, Med. Klin. **122**:497-500, 1931.

11. Reschke, K.: Lumbar Ramisection for Causalgia in an Amputation Stump of the Thigh, Internat. Abstr. Surg. **59**:504-505, 1934.

Shaw,[12] have asserted that pain impulses from the periphery do traverse the sympathetic ganglions. Many of the data tending to indicate that afferent neurons may enter the sympathetic chain by way of the gray rami from the mixed nerves or by following major blood vessels proximally have been secured in a study of human subjects under clinical conditions. The surgical clinic has obvious disadvantages for the conduct of controlled experiments, but in a study of so subjective a phenomenon as pain it may be a more fertile source of information than the laboratory. At least, some of the clinical observations, such as the undeniable benefits occasionally conferred by periarterial sympathectomy, are most difficult to affirm or deny on the basis of animal experimentation. However, the great weight of experimental evidence is against the opinion that pain impulses from the periphery traverse the sympathetic ganglions. It indicates, rather, that they follow the mixed nerves, to enter the spinal cord by way of the posterior roots of the brachial plexus.

If one concedes that the relief of pain is not due to an interruption of afferent pathways, it is apparent that the effect must be attributable to an abolition of vasomotor impulses which have been contributing to the production of pain. Leriche[13] suggested in 1927 that relief of peripheral pain obtained by section of sympathetic fiber tracts might be due to some alteration of the blood supply acting on pain receptors of the somatic nerves. In the same year Sfameni and Lunedei[14] elaborated a somewhat similar theory. A more recent presentation of this same idea has been advanced by Davis and Pollock[15] in their discussions of "referred pain." That the vasomotor effects responsible for the phenomena of pain act on receptor *end organs* of somatic sensory neurons is implied by the following quotation from their paper:

> The impulses travel over preganglionic efferent fibers to the autonomic ganglions. A postganglionic fiber then carries the impulse to the skin, where sensory end organs are stimulated. Thus an ordinary somatic painful impulse is produced which travels over the spinal sensory nerves, enters the spinal cord by way of the posterior roots, and ascends in the lateral spino-thalamic tract to a cortical level.

It is difficult to make this theory apply to cases of fantom limb pain. The patients with this condition feel pain of specific quality and localiza-

12. Shaw, R. C.: Sympathetic System and Pain Phenomena, Arch. Surg. **27**:1072-1080 (Dec.) 1933.

13. Leriche, R.: Recherches et réflexions critique sur la douleur, Presse méd. **35**:497-499, 1927.

14. Sfameni, P., and Lunedei, A.: Sui refessi viscero-cutanei e sul mecanismo di produzione del dolore nelle affezioni dei visceri e delle sierose, Riv. di clin. med. **28**:758-766, 1927.

15. Davis, L., and Pollock, L. J.: The Rôle of the Autonomic Nervous System in the Production of Pain, J. A. M. A. **106**:350-353 (Feb. 1) 1936.

tion. It is relieved by interruption of the sympathetic pathways, but in this instance there are no sensory end organs in the parts where the pain is felt to originate. Since the limb has long since been amputated, it follows that pain ascribed to a particular finger cannot be due to any physiochemical changes in that finger acting on pain receptors of somatic sensory nerves.

One might assume that nerve fibers as well as end organs are capable of originating specific pain sensations when an adequate stimulus is supplied. When a sensitive neuroma is pinched a shocklike flash of pain may be felt in the area normally supplied by that nerve trunk, but such a pain has few of the characteristics of true fantom limb pain. A sensation similar to that produced by pinching a neuroma is caused by electrical or mechanical stimulation of exposed fiber bundles of mixed nerves, but there are lacking the specific characteristics of heat or cold, "tension," "tearing," "rawness" or "cutting" observed in fantom limb pain, and the pain is not referred to a particular part of a single digit. Attempts to stimulate a few fibers or even a single fiber have thus far failed to produce a specific or localized sensation. Yet it is possible that under experimental conditions the stimulus has not been adequate in quality and intensity, and that physicians have been led to the erroneous conclusion that specific sensations cannot originate in nerve fibers (in much the same way in which early investigators of visceral sensation were influenced to conclude that the viscera were entirely lacking in pain sensibility because they did not respond with sensations of pain to trauma or to thermal or chemical stimuli). Certainly it is difficult to avoid the conclusion that, whatever the pathologic physiology of fantom limb pain may be, the underlying exciting cause is to be found in the amputation stump. By no other means is it possible to account for the temporary alleviation of pain by compression of the arm with a sphygmomanometer cuff or by direct pressure over the principal artery; nor is it possible to account otherwise for the interval of relief from pain that may follow the resection of nerves or blood vessels or even the infiltration of the stump with a local anesthetic.

One can only speculate as to whether the trouble in the fibers is caused by compression of nerve trunks by scar tissue, by anoxemia and impaired nutrition, by direct stimulation of afferent neurones in the walls of damaged blood vessels or by some unknown physiochemical agent. Regardless, however, of the other factors which may aid in producing the syndrome of typical fantom limb pain, the nerve fibers in the stump undoubtedly are the ultimate exciting cause.

This point is well brought out in a study of the relation of the syndrome of fantom limb pain to other pain syndromes which suggest that nerve fibers have been irritated. I have in mind particularly causalgia (thermalgia), but there are also suggestive points of similarity to the

cervical rib syndrome, Volkmann's ischemic paralysis, the "protopathic" phase which may accompany nerve regeneration, and certain post-traumatic disturbances characterized by intractable pain.

In the irritative lesions of peripheral nerves there is usually observed a characteristic combination of symptoms. The pain is spontaneous and peculiarly unbearable; it tends to radiate; there are frequently associated sensations of cold or burning heat; hyperesthesia is almost invariably present; and, most striking of all, there occur vasomotor, sudomotor and trophic changes which indicate that reflexes involving the visceral nervous system have been called into play. Usually the disability which accompanies the irritative neural lesion is far greater than that which occurs when the nerve has been completely divided. This fact might be used to argue against the essential similarity of these conditions to fantom limb pain, because in patients suffering from such pain the nerves have, of course, been completely severed; but it does argue that lesions which involve nerve fibers are capable of setting off a train of serious and disabling symptoms.

I say "setting off a train of symptoms" because I believe that the initial lesion is merely the percussion cap that leads to the detonation of the main powder cache. In a former writing [3] I said: "It seems probable that the injury to certain tissues starts a cumulative process which is not confined to the single nerve distribution and which tends to spread to involve the spinal cord in diffuse reflex phenomena in which the sympathetic nerves are prominently affected." The interval of time that frequently elapses between the injury and the onset of the pain, the period of relief that may follow the division of nerves at higher levels and the increasing momentum of all the associated phenomena suggest that a vicious circle of reflex activity is present. Unquestionably, the sympathetic nerves form an important link in the vicious circle. Once the sympathetic nerves are involved, anything that adds to their activity, whether it be emotional distress, cold, barometric alterations or local injury, may augment the pain. Conversely, anything that lessens their activity, such as mental equanimity, physical relaxation, warmth and comfort, or careful guarding of the part, may diminish the intensity of the pain. Finally, anything that interrupts the sympathetic component of impulses may break the vicious circle temporarily. If the break is complete, a considerable period of time may elapse before the circle is established in its original intensity and the centers of the spinal cord and the brain are involved. If the circle is repeatedly broken, it may never reestablish itself effectively. I believe that in this rather vaguely expressed concept may lie the explanation of the fact that repeated injections of procaine hydrochloride near the sympathetic ganglions have "cured" fantom limb pain in some cases.

It is possible that, as Leriche [1] has suggested, a certain "tissue susceptibility" in particular persons (just as some patients have a tendency to keloid changes in surgical scars while others have not) may be a factor in determining whether with irritative neural lesions they will have causalgia or whether after having an amputation they will suffer fantom limb pain. Without doubt, the temperament of the patient has much to do with his reaction to pain. It is also possible that showers of afferent impulses from the periphery may hypersensitize the spinal cord or the brain centers, or that garbled messages from the stump may be misinterpreted by the thalamic centers, so that, as Stopford [16] has suggested in the case of protopathic pain, there may be overreaction and exaggeration. Yet it seems to me wholly unreasonable to conclude that because a particular patient suffers from causalgia or fantom limb pain while another with an apparently similar lesion does not the patient with painful symptoms is therefore neurasthenic and his trouble is not amenable to any but psychic therapy. There should be sympathy and understanding as well as unsparing effort to relieve the suffering of these unfortunate persons, even though physicians' insight into the mechanisms responsible for the pain is still obscured.

SUMMARY

The syndrome of fantom limb pain is a definite clinical entity.

Its symptoms may be temporarily alleviated in many instances by injections of procaine hydrochloride in the region of the thoracic sympathetic ganglions.

Occasionally, the relief afforded by such an injection persists for a long time.

The observations here reported suggest that the present interpretation of the influence of the sympathetic nerves on pain of peripheral origin may require modification.

16. Stopford, J. S. B.: Sensation and the Sensory Pathways, London, Longmans, Green & Co., 1930.

OSTEOMYELITIS OF THE PELVIC GIRDLE

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Like all other bones of the skeleton, the component parts of the pelvic girdle are subject to the occurrence of foci of osteomyelitis. It is found that the forms of osteomyelitis usually resulting from or associated with various kinds of trauma are more prevalent than the orthodox hematogenous forms resulting as thromboembolic phenomena in the course of a general infection (sepsis, pyemia or bacteremia).

ANATOMY

The pelvic girdle is composed of two main divisions: (1) the sacrum [1] and (2) the innominate bone. The sacral vertebrae conform in structure, external form and physiologic function with the other bones of the spine, except that they are fused during adolescence to form the adult entity known as the sacrum.

The innominate bone is one of the most irregular bones of the body. The external physical form of its major segments resembles that of all the other bones of the skeleton, including the long bone, the flat bone and the irregular bone proper. Nevertheless, its intimate structure is essentially that which is seen in the true irregular bone, such as the vertebra or the maxilla, and consists of an outer thin plate of compact osseous tissue surrounding and enclosing an interior mass of cancellous tissue. Nowhere is there a suggestion of a marrow cavity. In the parts where function demands broad surfaces and a thin platelike structure, the cancellous tissue disappears entirely, and only the two opposing layers of compact bone tissue remain, fused in a thin plate. This is especially noticeable at the bottom of the acetabulum and in the center of the iliac flare. During the development of an osteomyelitic focus perforation of these thin parts of the bone is relatively common.

The entire structure is covered by a well developed periosteum (to which the various muscles are attached) except for certain areas. Along the crest of the ilium, over the anterior and especially the posterior iliac spine and over the anterior surfaces of the rami of the pubis

1. As the subject of osteomyelitis of the spine has been thoroughly discussed on another occasion, I shall not include any extensive discussion of osteomyelitis of the sacrum in this communication except where it is found necessary because of its association with osteomyelitis of the innominate bone proper.

and the ischium the attachment of the muscles makes for deep anchorages, which disturb somewhat the distinctness of the individuality of the periosteal membrane. This is necessary because of the physiologic function of these muscles. At the symphysis pubis and at the sacroiliac synchondroses the periosteum disappears and is replaced by a thin layer of cartilage; the entire structure at these areas is surrounded by thick ligamentous layers.

The Blood Supply.—The blood supply of the pelvic girdle comes from the periosteal plexus, which is formed by a number of supply vessels perforating the periosteal layers at various points. A distinct nutrient vessel commonly perforates the outer side of the ilium between the crest and the anterior and posterior gluteal lines. On the inner side the iliac branch of the inferior gluteal artery perforates the bone under cover of the iliacus muscle.

The obturator artery passes forward and downward on the lateral wall of the pelvis to the upper part of the obturator foramen. Inside the pelvis it gives off iliac branches to the iliac fossa, which supply the bone and the iliacus muscle; it has also a pubic branch, which ascends on the back of the pubis, communicating with the corresponding vessel of the opposite side and with the inferior epigastric artery. Outside the pelvis the obturator artery, by its posterior branch, follows the posterior margin of the foramen and turns forward on the inferior ramus of the ischium, where it anastomoses with the anterior branch. It supplies an articular branch which enters the hip joint through the acetabular notch, ramifies in the fat at the bottom of the acetabulum and sends a small branch along the ligamentum teres to the head of the femur. The internal pudendal artery gradually approaches the margin of the inferior ramus of the ischium and passes forward between the two layers of the fascia of the urogenital diaphragm; it then passes forward along the medial margin of the inferior ramus of the pubis.

According to Lexer, Kuliga and Turck, the most important part of the blood supply goes to the ilium. The most important vessel perforates the inner side of the ilium near the posterior end of the arcuate line and proceeds forward, upward and anteriorly toward the flare of the bone. Many branches proceed toward the iliac crest. Relatively large vessels supply the upper ramus of the ischium and proceed backward in the general direction of the sacroiliac synchondrosis. Little change in the arrangement of the blood vessels occurs as the person grows older.

The blood supply is at a minimum where the bone is thinnest and consists of compact bone solely; it varies in other parts of the bone with the extent of the cancellous structure, and in young persons it is most abundant in and around the centers of ossification. Here the

vascular loops are to all intents and purposes end vessels. The most abundant supply is in the general neighborhood of the acetabulum and the junction of the three segments of the innominate bone. Clinically this corresponds to the more frequent localization of foci of osteomyelitis in these areas.

An extraordinary fact in this ensemble is the relatively small blood supply as compared with that of other bones. Possibly this is the most important single factor which contributes to the relatively small number of foci of osteomyelitis which occur in the pelvic girdle, for poverty of vascular channels would give small opportunity for the establishment of thromboembolic foci.

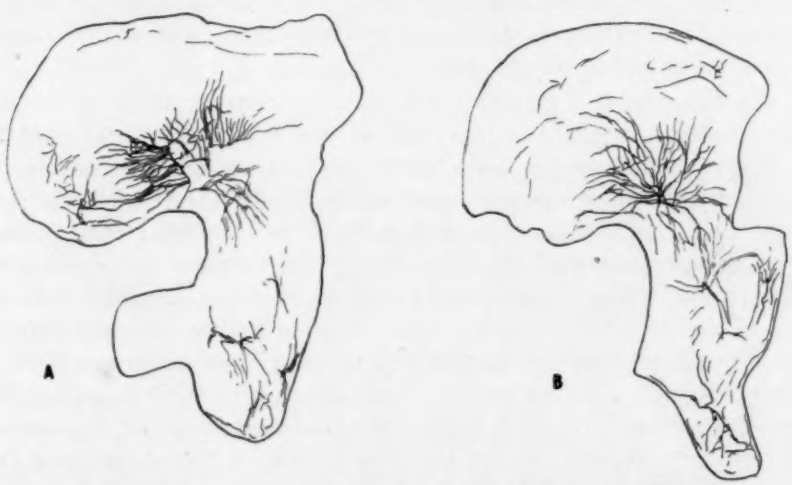

Fig. 1.—Blood supply of the innominate bone; semidiagrammatic, after E. Lexer, P. Kuliga and others (Untersuchungen mittelst Röntgenaufnahmen injizierter Knochen und ihre Bedeutung für einzelne pathologische Vorgänge am Knochensysteme, Berlin, A. Hirschwald, 1904). *A*, view sketched from the outer side of the bone. *B*, view sketched from the inner side of the bone.

Development and Ossification.—According to Gray's "Anatomy":

. . . the hip bone is ossified from eight centers: three primary—one each for the ilium, ischium, and pubis; and five secondary—one each for the crest of the ilium, the anterior inferior spine, the tuberosity of the ischium, the pubic symphysis and one or more for the Y-shaped place at the bottom of the acetabulum. . . . At birth, the three primary centers are quite separate. The others . . . being still cartilaginous. By the seventh or eighth year, the inferior rami of the pubis and ischium are almost completely united by bone. About the thirteenth or fourteenth year, the three primary centers have extended their growth into the bottom of the acetabulum, and are there separated from each other by a Y-shaped portion of cartilage, which now presents traces of ossification, often by two or more centers. One of these, the os acetabuli, appears about the age

of twelve, between the ilium and pubis, and fuses with them about the age of eighteen; it forms the pubic part of the acetabulum. The ilium and ischium then become joined, and lastly the pubis and ischium, through the intervention of the Y-shaped portion. At about the age of puberty, ossification takes place in each of the remaining portions, and they join with the rest of the bone between the twentieth and twenty-fifth years. Separate centers are frequently found for the pubic tubercle and ischial spine, and for the crest and angle of the pubis.

Clinically, the various centers of ossification are important because terminal loops (that is, end arteries) are present in the areas surrounding the centers of ossification. They form points of election for the formation of thromboembolic foci, and in actual practice foci of osteomyelitis are found to develop most frequently in these areas and in association with the abundant vascular plexus found in the neighborhood of centers of ossification.

Physiology and Function.—The most important function of the pelvic girdle is mechanical; the bone serves to transmit the weight of the trunk and the upper limbs to the lower extremities. The underlying principle of the general architecture of the pelvic girdle is that of the arch. The obliquely lateral curve of the innominate bone proper corresponds to the sides of the arch, and the sacrum corresponds to the keystone. The various stresses and strains are so disposed that the lines of force also correspond to a series of arches obliquely superimposed one on the other. In this way the maximum amount of physiologic purpose is achieved with a minimum of structural material. In order to lessen concussion in rapid changes of distribution of the weight, the sacroiliac articulations are interposed between the sacrum and the iliac bones, and the pubic symphysis exists in the middle of the anterior arch.

During pregnancy the pelvic joints and ligaments are relaxed and are therefore capable of extensive movements. When the fetus is being expelled the force is applied to the front of the sacrum. Upward dislocation is again prevented by the interlocking mechanism of the middle segment. As the fetal head passes the anterior segment the latter is carried upward, enlarging the anteroposterior diameter of the pelvic inlet; when the head reaches the posterior segment this also is pressed upward against the resistance of its wedge, the movement being possible only by the laxity of the joints and the stretching of the sacrotuberous and sacrospinal ligaments.

CLASSIFICATION OF FORMS OF OSTEOMYELITIS FOUND CLINICALLY

Primary, extension and hematogenous forms of osteomyelitis occur in the bones of the pelvic girdle. As a general rule, the number of cases of the primary and extension forms of osteomyelitis exceeds

the number of those in which the condition is due to hematogenous infection. Frequently there is a certain amount of association of the mechanisms causing the primary and extension forms, so that it is difficult clinically to differentiate accurately between the two. The difficulty exists especially with conditions occurring after trauma or after a surgical operation. When the physical objective signs of the infection of bone occur immediately there is little doubt that the process is a primary osteolytic infection. When some time elapses between the operation and the demonstration of the osteomyelitic process, one of two explanations is possible: 1. The process may have started immediately but with so few subjective and objective symptoms that the infection of the bone was not observed until it had passed into the chronic stage. Such a process is still a primary infection of bone, that is, primary osteomyelitis. 2. Infection may have developed in the soft parts and a steady progression of the process occurred until the bone was secondarily involved and the condition was recognized clinically some time later. This is the extension form of osteomyelitis. The following description of the primary and extension forms of osteomyelitis of the pelvic girdle is made with this reservation in mind.

In cases of hematogenous infection there is practically never any difficulty clinically in determining the pathogenic origin.

PRIMARY OSTEOMYELITIS OF THE BONES OF THE PELVIS

Primary osteomyelitis of the pelvic girdle is always a consequence of trauma and necessarily follows the production of an open wound which communicates with the bones. Though a gross fracture is usually demonstrable, it is not necessarily so; a stab wound may traverse the overlying soft parts and penetrate the bone, or a bullet may cause a groove in the surface of the bone. In compound fractures the communication may extend to the skin, to the interior of the bladder or bowel or to the surface of the vagina. In civil life the commonest form of compound fracture extends into the bladder; in comparison with this, compound fracture into the skin or into the rectum is uncommon. Communication with the vagina is somewhat more common. Primary or secondary infection of the bone as a consequence of compound fracture into the bladder is most unusual, because operation is almost always immediately necessary and modern technic requires closure of the bladder wound and drainage of the bladder through the urethra by catheter. If because of the situation of the bladder rupture (for example, if it occurs at the neck of the bladder) immediate closure of the bladder is impossible, the drainage of urine is established by the suprapubic route; the extension form of osteomyelitis occasionally follows, as will be pointed out later.

In both civil and military traumas of large degree, as, for instance, when a fall from a great height causes extensive shattering of the pelvic girdle with compounding of the fracture either externally or internally, or in wounds caused by shrapnel and shell with equally extensive loss of tissue, the injury is commonly of such importance as to cause death either immediately or very shortly. Under such conditions, osteomyelitis does not have any opportunity to develop.

In civil and military life wounds produced by similar objects (that is, bullet wounds and stab wounds) are essentially similar. Troops in active engagement, however, are handicapped by fatigue, by undernourishment, by the filthy conditions of field warfare, by the extraordinary likelihood of fecal contamination of any and every wound, by the frequent inclusion of foreign bodies (for example, pieces of clothing) in the wound and by delay in receiving adequate medical and surgical attention.

The treatment for these forms of injury is essentially prophylactic and is planned to prevent infection of any kind in any part of the tissues involved in the injury; naturally, this also includes the prevention of any infection in the osseous tissue. In differentiating between the injuries occurring in civil life and those occurring in military life it will be found that the necessary débridement is more extensive with the latter class of injuries than with the former. Except for this the treatment, prophylactic and otherwise, is the same in either class. In cases of injuries communicating with the intestinal tract it is advisable to administer prophylactic doses of gas gangrene and tetanus antitoxin.

Primary infection of the pelvic girdle complicates operations on the bone itself, on the tissues in contact with it or on the organs housed in the pelvis when the surgical procedure necessitates baring of the osseous structure or resection of portions of it. The two commonest varieties of infection occur with operation for sacral dermoid cyst and with the sacral or perineal type of operation for carcinoma of the rectum.

Osteomyelitis Following Operation for Excision of Sacral Dermoid Cyst.—I have seen several persons in whom a superficial form of osteomyelitis of the sacrum followed excision of an infected sacral dermoid cyst. Clinically these infections of the bone served to inhibit the healing of the wound for a much longer period than was normal. In no instance was a revision of the wound found necessary.

Osteomyelitis Following the Sacral Type of Operation for Carcinoma of the Rectum.—In the sacral (Kraske) and in the perineal form of operation for carcinoma of the rectum all the factors just referred to are present. A common postoperative complication is a necrotizing infection of the soft tissues attached to the sacrum. This infection

occasionally is extensive enough to pass around the great sacrosciatic notch and involve the ilium; the necrotized tissues become black, and gas is frequently produced. When the patient is able to withstand the immediate effects of the operation and the subsequent effects of the intense necrotizing inflammation, the eventual separation of the dead and sequestrated tissue commonly reveals that the infection has passed into the underlying bone, and frequently small sequestrums are extruded.

In the sacral operations and in a few of the perineal operations in which the coccyx alone is excised, there is usually an immediate infection of the bone at the line of section. Some, at least, of the extraordinary length of time necessary for the healing of the wound undoubtedly must be referred to the infection of the bone.

The infection found complicating perineal operations is undoubtedly an immediate infection, or primary osteomyelitis. The type of infection which complicates sacral operations partakes of the mechanism of both primary and secondary infection of the bone.

The treatment of either of these forms of osteomyelitis when the condition occurs as a complication of operation is conservative.

EXTENSION FORMS OF OSTEOMYELITIS OF THE PELVIC GIRDLE

Extension forms of osteomyelitis of the pelvic girdle also follow as a complication of the clinical events outlined in the previous sections. In clinical practice the following varieties are found in addition.

Osteomyelitis of the Pubis Following Suprapubic Cystotomy.—In this clinical syndrome there is apparently a mild form of infection customarily indicated by the term "periostitis" or "osteitis." It occurs after operations in which the bladder is opened, and subsequent urinary drainage occurs through a suprapubic fistula for the usual considerable length of time. The operations are commonly done for hypertrophy of the prostate, for malignant tumor and occasionally for stone. The development of the pathologic process in the bone is aided by the necrotizing effect of the irritating and infected urine on the soft tissues attached to the symphysis pubis. The bone is secondarily bared and infected after the separation from it of the necrotic soft tissue. In this extension condition infection in the osseous tissue is aided by injury to the periosteum or to the bone, by continued traction of the muscles attached to the bone and most of all by necrosis of the margins of the drainage tract caused by pressure of the tube or other drainage apparatus. Diabetes when it exists is a powerful adjuvant factor. In cases in which a malignant lesion is present the undernourished condition of the tissues is also an important factor.

In the literature there are only a few references to this complication of suprapubic cystotomy. There are references to it by Cabot in his

"System of Urology," by Lazarus [2] and by Beer.[3] Beer's paper from the Mount Sinai Hospital, New York, includes reports of 3 cases in which the condition was positively identified and a reference to "numerous other similar cases." Lazarus' experience included the observation of 3 cases. In 1 of these the lesion was proved roentgenologically to be extensive. This should not mislead any one into taking it for granted that this complication is rare. It is so easy to fail to recognize the clinical fact of this lesion's occurrence in what may be a large, foul and badly infected wound that many more such lesions actually occur than are recognized or reported. The extensive lesions are recognized; the lesser ones, lesser both in extent and in clinical disturbance of postoperative convalescence, are lost because of the physician's negligence or because of his inability to recognize the subjective and objective symptoms.

The clinical picture of this complication is usually definite. Because of the situation of the osteomyelitis in the symphysis, the pubis and the neighboring rami, the outstanding symptoms are pain over the lower attachments of the rectus abdominis muscle, over the body, symphysis and rami of the pubic bone and over the inner aspects of the thighs with spasm of the adductor muscle, so that the patient finds it painful to walk, to spread the thighs and to cough. Late symptoms are pain on defecation and terminal dysuria. Fever may be present in the early stages of the complication, but even then it may not be properly referred and integrated because of the original disease and operation. Any suppuration referable to the osseous lesion is unrecognizable clinically in the usual discharge from the wound, diluted as it always is in the escaping urine (see section on hematogenous osteomyelitis of the pubis).

In the early stages of the lesion roentgen examination may yield entirely negative results or may reveal an inconclusive fraying of the edges of the bone. In extensive lesions in a later stage there are definite areas of absorption which leave little doubt that some extensive lesion has occurred. In the absence of a malignant condition the diagnosis can be definitely made of an inflammatory lesion, that is, osteomyelitis. In the presence of a malignant condition the diagnosis is not quite so simple, and differentiation must be made from metastatic deposits in the bone. Also, it is conceivable that the two lesions may coexist.

Osteomyelitis of the pubis is usually a self-limited complication of suprapubic cystotomy. The treatment should usually be palliative, expectant and conservative. Naturally, the sinus will not close until the condition of the bone is normal, but in the reported cases a permanent fistula has rarely, if ever, occurred. In cases in which the lesion

2. Lazarus, J. A.: Ann. Surg. **103**:310, 1936.
3. Beer, E.: J. Urol. **20**:233, 1928.

is extensive sequestration may take an untoward length of time, and in some the time of healing and convalesence may be shortened by revision of the wound. Ordinarily the time of healing varies, according to the extent of the lesion, from two to six months.

Osteomyelitis of the Pubis Occurring After and Complicating Symphysiectomy in Obstetric Cases.—In a review of the literature up to 1934 Jentzer [4] could find only 1 case of this kind. None of several obstetricians whom I consulted could recall a similar case in his experience. Jentzer's experience consists of the observation of a single case.

Jentzer's patient, a woman aged 29 who had never been seriously ill, was subjected to symphysiectomy during a difficult delivery. About two weeks later she complained of pain in the pelvis, and there was a discharge from the wound over the symphysis. When she began to walk she felt agonizing pain in the region of the pubis, and her gait resembled that caused by bilateral congenital dislocation of the hip. Her condition gradually became worse. About five months after the delivery, when she was first seen by Jentzer, roentgen examination of the pubis showed separation of the symphysis for about 20 mm., destruction of bone, rough edges and small sequestrums. Operation was followed by complete recovery.

I was able to find an additional case in the records of Söderlund.[5]

In Söderlund's case the patient was a woman who had had an uncomplicated labor and who complained thereafter of pain radiating down the right lower extremity which continued during the puerperium. The pain increased progressively during the next one and one-half years, and eventually it also radiated to the right hip. A vaginal discharge appeared early, continued and was finally traced to a sinus which communicated with the os pubis. This led to the correct diagnosis. After sequestrotomy the symptoms promptly subsided.

HEMATOGENOUS OSTEOMYELITIS OF THE PELVIC GIRDLE

Except for its location and some factors peculiar to this location, hematogenous acute osteomyelitis of the bones of the pelvic girdle differs in no way from similar forms of osteomyelitis in any of the other bones of the skeleton. All the facts applying to the etiology, bacteriology, mechanism of infection, pathology and pathogenesis which I have described and discussed on many previous occasions, and have also included in my book,[5a] apply to hematogenous acute osteomyelitis of the bones of the pelvis.

The groups of reported cases found in the literature are summarized in table 1.

The Mount Sinai Hospital series contained 346 cases of osteomyelitis of all types and of all the bones of the skeleton. The patients were

4. Jentzer, A.: Rev. d'orthop. **21**:289, 1934.

5. Söderlund, G.: Acta chir. Scandinav. **67**:850, 1930.

5a. Wilensky, A. O.: Osteomyelitis: Its Pathogenesis, Symptomatology and Treatment, New York, The Macmillan Company, 1934.

admitted to the hospital between 1926 and 1932. There were 12 cases of hematogenous osteomyelitis of the pelvic bones. The distribution is shown in table 2. I have had 1 private case of hematogenous osteomyelitis of the ilium in which the condition occurred in a patient with

TABLE 1.—*Cases of Hematogenous Osteomyelitis of the Pelvis Reported in the Literature*

Author	Location of Lesion	Number of Cases	Total Cases Osteomyelitis	Total Lesions
Klemm, P.: Die akute und chronische infectiöse Osteomyelitis des Kindesalters auf Grund eigener Beobachtungen und Untersuchungen, Berlin, S. Karger, 1914	Ischium Pubis	2 2	320	385
Lloyd, E.: Proc. Roy. Soc. Med. **21**: 1387, 1928	Pubis and ischium	2	29	
Ogilvie, W. H.: Proc. Roy. Soc. Med. **21**: 1390, 1928	Pubis	1	51	
Platt, H.: Proc. Roy. Soc. Med. **21**: 1378, 1928	.....	0	41	
Doran, W. T., and Brown, L.: Surg., Gynec. & Obstet. **40**: 658, 1925	Ischium	3	71	
McWhorter [10]	Pubis and ischium Ischium	1 3		
Raeschke: Klin. Wchnschr. **7**: 72, 1928	Pubis	1		
Phemister, D. B., cited by McWhorter [10]	Pubis	1		
Kulowski [6]	Sacrum and ilium	9		
Isen [7]	Pubis	3		

TABLE 2.—*Location of Pelvic Bone Lesion in Cases of Hematogenous Osteomyelitis*

Location of Lesion	Cases	Total Lesions
Pubis	1	3
Bilateral pubis (symphysis)	1	
Ilium	5	
Ilium and bilateral pubis (symphysis)	1	4
Ischium	2	
Sacrum	2	2

TABLE 3.—*Age Distribution in Cases of Hematogenous Osteomyelitis*

Age	Number of Patients
1 to 10 years	2
11 to 20 years	4
21 to 30 years	1
31 to 40 years	0
41 to 50 years	1
51 to 60 years	4

two other osteomyelitic lesions. There were 7 male and 5 female patients in the series of 12 cases. The age distribution is shown in table 3. It seems a little extraordinary that 5 of the patients should have been above 30 years of age; this is a variation from the age incidence in cases of hematogenous osteomyelitis of the other bones of the skeleton.

Bacteriologic studies are available in 2 of these 12 cases. In 1 case the lesions yielded Staphylococcus aureus; in the other they yielded Streptococcus haemolyticus. In both of these cases the blood culture was positive.

Pathogenesis and Pathology.—The pathologic picture, pathogenesis and mechanism of hematogenous acute osteomyelitis in the pelvis are exactly similar to those of the same condition in the other bones of the body and are based on the formation of a thromboembolic lesion in the vascular plexus of the bone. Because of the essential anatomic and vascular conditions there is no repetition of the typical distribution seen in the long bones, and the lesions produced in the pelvic bones are of irregular size and shape and are determined by the anatomic arrangement of the blood vessels. In the pubis and ischium the lesions vary from concentration in inconsequential segments to involvement of nearly the entire anatomic segment. In the ilium the lesions most often are in the neighborhood of the acetabulum or along the crest; in the flare of the ilium complete development of the lesion is commonly followed by oval or circular deficiencies in the bone structure. Periosteal lesions are as common as lesions involving the entire thickness of the bone.

General Symptoms.—The general symptoms and course of acute hematogenous osteomyelitis of the bones of the pelvis differ in no way from those present when the disease attacks other bones of the skeleton. This is especially exemplified when multiple lesions are present and when one or more of these are located in the pelvis. The several classifications into hyperacute and moderately severe infections obtain in cases of pelvic localization as well as in others.

In the hyperacute condition the clinical picture is that of a profound and overpowering infection and intoxication of the entire system. There are initial chills and subsequent high fever, and the general condition rapidly becomes alarming. Blood cultures are positive as a rule. The signs of any local disease are at a minimum, are frequently absent, and when present and looked for are not easily demonstrable, owing to the tremendous intoxication which is present. With the most severe forms death follows in a few hours from the general infection. From the severe and dramatic forms, all grades of intensity of infection exist, down to those described in the following sections.

In cases in which the condition is very severe the diagnosis is frequently in doubt beyond the bare fact of the presence of a general infection. Erroneous diagnoses are common: frequently the disease is assumed to be typhoid fever, or because the character of the symptoms is influenced by the rapid development of some complication within the meninges it is thought that cerebrospinal meningitis is present. Examples of this kind are numerous in the literature.

Fig. 2.—Perforation of the flare of the ilium after osteomyelitis.

Fig. 3.—Osteomyelitis of the flare of the ilium extending down to the acetabulum. (Supplied by Dr. Farr.)

The differentiation of osteomyelitis from other diseases is not, moreover, the sole diagnostic difficulty. It is also extremely difficult to determine whether the osteomyelitic focus exists in those segments of the innominate bone which are anatomically distant from the iliac flare and crest, whether it is located in the hip joint or whether it is to be found in the head or neck of the femur. Even when local symptoms of pain and tenderness, general tumescence and limitation of motion are present this difficulty is not lessened. Roentgenographic studies do not give any indication of the location in the first ten days of the infection and are therefore of no help. An illustrative case is the following one from the records of the Mount Sinai Hospital:

A boy was admitted with symptoms of a severe infection and with local signs pointing to the general region of one hip. Because it was not possible to locate the focus accurately, I decided to follow the conservative method of treatment and not to operate. This treatment gave satisfactory results, and operation was never done. Several months later there was roentgenographic and clinical proof that the focus was in the lower ramus of the pubis. The possibility of this localization had not occurred to me or to any of my associates at the time the patient was admitted to the hospital.

Local Symptoms.—The local signs present special characteristics according to the segment of the pelvic girdle which is involved. These may be referred (1) to the sacrum, (2) to the sacroiliac region, (3) to the flare of the ilium, (4) to the central acetabular region, (5) to the pubic bone or (6) to the ischium.

I. HEMATOGENOUS OSTEOMYELITIS OF THE SACRUM

At an early stage of hematogenous osteomyelitis of the sacrum the patient shows a tendency to assume the supine posture. Tenderness and rigidity of the lower end of the spine are present. In a few days the following local signs point to the actual seat of disease:

Local Swelling.—When the lesion is in the posterior aspect of the sacrum the signs consist in the development of a widespread and indefinitely demarcated edematous swelling and tenderness over the appropriate part of the sacrum. The swelling is usually not detected before the third or fourth day, and in some of the recorded cases it was detected even later. A striking characteristic is the widespread area of the soft parts affected as compared with the extent of the affected area in the bone.

When the process is in the anterior part of the bone and shows a tendency to point anteriorly, there is little, if any, external evidence of the existence of infection in the bone. In cases of severe involvement the nature of the illness is lost, and a diagnosis of typhoid fever or of meningitis is often made; in some cases, indeed, the true diagnosis

is made only after death. Rectal examination is the most important part of the physical examination. The elicitation of tenderness and the palpation of the subperiosteal abscess which invariably forms in the hollow of the sacrum should lead to a correct diagnosis.

Local Pain.—In cases in which the condition is less severely toxic pain is an important symptom. The pain is of two kinds, spontaneous and provoked. Spontaneous pain varies in different cases. Pain provoked by pressure over the affected area has great diagnostic value and permits the location of the process to be determined at a relatively early stage of the disease.

II. HEMATOGENOUS OSTEOMYELITIS OF THE SACRUM AND ILIUM SURROUNDING THE SACROILIAC JOINT

Attention has recently been called to the form of hematogenous osteomyelitis which is found in the ilium and sacrum surrounding the sacroiliac joint. Kulowski's [6] report discussed an incidence of approximately 30 cases in Steindler's clinic in the State University of Iowa. The report is somewhat obscure, because it is difficult to distinguish from the descriptions given whether the process began in the joint, in the sacrum or in the ilium; furthermore, Kulowski spoke of "osteomyelitis of the sacroiliac joint," which is obviously a misnomer.

The following are the pathogenic possibilities:

A. The process may begin as an infection solely of the joint. It is a common experience to find clinical evidence of disease in the joint but roentgenographic evidence proving that there is no involvement of any part of the bone contiguous to the joint. In most lesions of this origin the bone remains uninvolved.

B. The process may begin in the bone, either in the sacrum or in the ilium. Involvement of the joint occurs secondarily. Kulowski stated that once the joint is involved extension occurs rapidly and almost inevitably from one bone to the other, making the lesion a total one, and that this is the usual progression of the lesion.

C. The vascular lesion may be such as to involve the joint and the bone simultaneously.

By the time the lesion is definitely established and clinically recognized, both joint and bone are usually involved. Destruction of osseous tissue in the sacrum is much more serious, functionally, than is similar destruction in the ilium. From Kulowski's report it appears that sclerotization readily occurs in the thin plate of the iliac flare and limits to a certain extent the spread of the lesion in that direction.

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6. Kulowski, J.: Am. J. Surg. **23**:305, 1934.

Symptoms.—A careful history should not fail to call attention to the general region of the sacroiliac joint. The rapidity of onset and the development of the subjective and objective symptoms vary with the individual patient. Pain is always present and is not usually relieved by any change of posture. There may be radiation of the pain along the sciatic distribution, and in some cases it is referred to the hip. Spasm of the iliopsoas muscle is present. Objectively the extent and principal location of the lesion are difficult to determine. Except in the presence of an external accumulation of pus, the external tissues merely show

Fig. 4.—Osteomyelitis of the sacroiliac region. This is the extension form of osteomyelitis. (Supplied by Dr. Frank E. Meleney.)

edematous induration. Tenderness over the joint and the adjacent parts is marked.

Retroperitoneal irritation is frequently present. It shows itself by spasm of the iliopsoas muscle and by symptoms referable to the bowel and to the lower segments of the genitourinary tract.

Roentgenographic study usually reveals no definitive data in the early stages of development of the lesion. Later there are abundant evidences of more or less destruction of osseous tissue and disorganization of the sacroiliac joint, and when the lesion is unilateral the differences are striking.

Formation of Abscesses in Sacral and Sacroiliac Osteomyelitis.—Abscesses and abscess extensions of the most bizarre type may develop, and these tend sometimes to mislead the physician as to the site of the original focus. According to the location of the lesion, abscesses may occur on the anterior or posterior aspect of the bone or, more rarely, on both, and sometimes suppuration occurs in the interior of the terminal part of the spinal canal.

1.—*Lesions Developing on the Posterior Aspect of the Sacrum.*—Suppuration occurs in a line with one of the spinal gutters. The symptoms are distinct and are those of an abscess in the tissues over the sacrum; the diagnosis is not difficult, and associated processes do not appear. Liquefaction may not occur until a week or more has passed. When the abscess is opened denuded bone is usually detected at the bottom.

2.—*Lesions Developing in the Parts of the Sacrum Bordering the Terminal Part of the Spinal Canal.*—These lesions are apt to cause exudates in the interior of the spinal canal, which vary from extradural solid exudates to extradural abscesses and occasionally to intradural infections, that is, to spinal forms of meningitis. With the former the local neurologic symptoms assume the characteristics of syndromes usually associated with pathologic conditions of the sacral and coccygeal nerves (that is, the cauda equina syndrome). In cases of meningitis the meningeal symptoms dominate the picture.

3.—*Lesions in the Sacrum Situated Anteriorly.*—These lesions produce subperiosteal abscesses on the anterior surface of the hollow of the sacrum. They spread laterally and downward toward the inferior aperture of the pelvic girdle and are more or less easily palpable by rectum. The folowing paths can be distinguished anatomically:

(*a*) One form of lesion develops from the lower segment of the sacrum or from the coccyx. Suppuration from this source gathers in the interval between the coccyx and the anus and lies beneath the levator ani muscle and the anal fascia. Occasionally the pus spreads out of the pelvic cavity through the sacrosciatic notch and is discovered in the depths of the gluteal muscles; more commonly the pus courses downward and appears clinically as a para-anal or pararectal abscess.

(*b*) Another type of lesion develops above the line of attachment of the levator ani muscle. In the larger number of such lesions a subperiosteal abscess develops on the inner aspect of the bone between the bone and the iliacus muscle and spreads upward to the crest of the ilium, where it appears as an extraperitoneal abscess. In some cases the abscess points above Poupart's ligament. In a lesser number of cases an abscess forms which spreads forward and downward in the hollow of the sacrum and between the bone and the obturator and recto-

vesical layers of the pelvic fascia. The pus gathers in the ischiorectal fossa and appears clinically as a high ischiorectal abscess. In some cases an abscess spreads upward, so that it cannot be palpated from below through the rectal and/or the vaginal canal or is palpable with great difficulty. This is the type of abscess which most frequently appears clinically as an obscure form of general infection (pyemia or sepsis).

In all the pelvic varieties of abscess the entire abscess lies within the pelvis. It is of the utmost importance to remember that the abscess is palpable by either rectal or vaginal examination or both. The ability to obtain the maximum amount of information by pelvic examination must be developed in order to treat lesions of this type.

For purposes of treatment the abscesses can be grouped as (*a*) high pelvic abscesses, (*b*) ischiorectal abscesses and (*c*) para-anal abscesses. The last mentioned are the simplest. Ischiorectal abscesses should be allowed to come down as far as possible; their proper incision is then much simplified. High pelvic abscesses are difficult to incise. In a certain number resection of the coccyx and possibly of the lowermost part of the sacrum is necessary in order to secure adequate drainage. The difficult ones are those which pass out of the pelvic cavity and point in a superficial location, as do some of the gluteal abscesses. The rule is to suspect an intrapelvic origin for any gluteal abscess in which there is retention of pus and which shows any tendency to retarded healing.

III. OSTEOMYELITIS INVOLVING THE FLARE OF THE ILIUM

Osteomyelitis of the flare of the ilium may point externally, in which case the pathologic condition is found principally in the tissues covering the external side of the bone. All the usual symptoms, of pain, tenderness and disability, are present; swelling is proportionate to the extent of the process and to the size of the subperiosteal abscess which forms under cover of the gluteal muscles. When the process is demarcated toward the internal visceral aspect of the bone the symptoms are referred to the loin, to the lower part of the abdomen and to the pelvis. Subperiosteal abscesses form under cover of the iliacus muscle and the tendon of the psoas muscle. Progression of the abscess may be upward, in which case the abscess points above the crest of the ilium or, in some cases, in a downward direction, toward the pelvic cavity. In the latter event the abscess is much more difficult to feel by rectum than are similar abscesses derived from the anterior surface of the sacrum.

A common complication and sequel is a perforation through the thin expansion of the flare of the ilium. Frequently this forms an insurmountable obstacle to the healing of the lesion until proper surgical measures are applied.

IV. OSTEOMYELITIS INVOLVING THE CENTRAL ACETABULAR REGION OF THE INNOMINATE BONE

In some cases any one or all of the acetabular parts of the ilium, the pubis and the ischium are involved. The following varieties are observable clinically:

A. In the first type the process in the bone is determined by the vascular distribution (see section on blood supply) of the lesion on its external aspect. Almost from the beginning the process is intracapsular, the joint is involved in the suppuration and the clinical picture is dominated completely by the symptoms of the joint involvement, even when additional pathologic conditions are plentifully present external to the joint capsule (for example, suppuration and sequestration in the extracapsular portions of the bone close to the joint).

The general symptoms are apt to be most prominent in cases in which the condition is of only ordinary severity, even when no overpowering general infection is present. The temperature is high, often reaching 105 or 106 F., and is apt to be sustained at those levels. Chills may occur. The blood cultures are usually positive during this stage. All of this is due to the retention of pus within the joint under increasing tension. Should the pus perforate the joint capsule and thread its way externally, the phenomenon of rupture is usually accompanied by amelioration of the general symptoms. Thereafter the temperature is variable, ranging usually from 101 to 104 F.

The local symptoms during the period of acuteness are pain, deformity, muscle spasm, diffuse swelling and tenderness in the general region of the hip. In some cases the pain is referred along the thigh to the knee. Movement is limited in all directions by muscle spasm, and pain is felt on any movement, especially when the leg is extended.

In the absence of a distinct abscess swelling is usually a general tumescence of the tissues of the hip surrounding the joint. This may be very slight. When the swelling is visible externally, rupture of the capsule and a secondary external abscess should be suspected, and the condition should be located, when possible, with the aspirating needle.

Local tenderness is almost always present anteriorly over the hip and posteriorly over the joint just behind the trochanter. Pelvic tenderness over the pelvic aspect of the acetabulum is usually slight, and no deformity of the contour of the bone at this area is felt during the pelvic (rectal) examination unless the suppuration succeeds in perforating the bottom of the acetabulum and spreading out beneath the pelvic periosteum and the pelvic fascia and between them and the bone. Such swellings are usually of moderate size because they drain into the joint and externally therefrom: usually, because of this fact, they need no special intervention and are resolved without treatment.

When the condition is acute there is flexion deformity of the thigh to the extent of an angle of about 40 degrees. Extension of the thigh when the patient lies on his back is accompanied by a definite downward tilting of that side of the pelvis. In addition, the lower limb on the involved side is rotated outward, and the knee is slightly flexed, in order to give the greatest comfort by relaxing the tissue and ligaments about the hip joint.

In this type of osteomyelitis it is usually impossible to tell from the general and local symptoms in which of the three segments of the central acetabular region the greater part of the osteomyelitic focus lies. Roentgenologic evidence is necessary to make the localization accurate.

The chief difficulty in differential diagnosis lies in the practical impossibility of distinguishing whether the lesion present lies in some part of the innominate bone or in the head or neck of the femur, whether the lesion is extracapsular or intracapsular or whether it is entirely a lesion of the joint. In the early stages this differentiation is impossible for lack of roentgenologic evidence; as soon, however, as roentgen aid is available this difficulty disappears.

Acute inflammatory rheumatism in the hip joint has many clinical resemblances to osteomyelitis. However, it is apt to be a polyarticular condition. The detection of a valvular or pericardial complication, so commonly found with acute articular rheumatism as to make its presence of diagnostic value, is of no clinical help in this differentiation, since similar lesions occur as a consequence of the general infection which precedes and accompanies acute osteomyelitis.

B. In the second type of osteomyelitis of this region the entire process remains extracapsular and never involves the joint. The general symptoms are approximately the same; the local symptoms show resemblance to those of foci of the type previously described, but they are ameliorated sooner, after which one can detect that the motions of the hip are relatively free. External abscesses appear, according to the location of the osteomyelitic focus, in each of the segments bordering the acetabular area.

C. Acetabular osteomyelitis of the third type is due to the situation of the lesion in the vascular channels supplying the visceral pelvic aspect of the acetabular region. The general symptoms are usually not as marked and are relatively benign; external swelling is nonexistent; and the characteristic local finding is a swelling on the pelvic side of the bone easily palpable by rectum and/or by vagina and situated opposite the joint. The swelling is a subperiosteal exudate or abscess. It is ordinarily of moderate size; and it rarely, if ever, perforates the joint across the thickness of the bone into the interior of the acetabulum. The "exudate" type of lesion is usually resolved spontaneously. The suppurative type does one of two things: It spreads upward and appears

above Poupart's ligament, or it spreads downward and, if large enough, assumes the characteristics of an ischiorectal abscess.

The lesion is usually easily demonstrable roentgenologically as a swelling corresponding to the palpatory findings on the inner aspect of the bone opposite the acetabulum.

V. OSTEOMYELITIS OF THE PUBIS

Chronic osteomyelitis of the pubis is found more commonly than the acute form, the reason for failure to recognize the process in its acute stage being that most pubic osteomyelitis is of the extension type in which the symptoms of the acute stage are lost in the manifestations of the original lesion to which the pubic osteomyelitis is secondary. In a review of the literature up to 1934 Jentzer was able to find a total of 16 cases of chronic hematogenous osteomyelitis of the pubis, in only 1 of which the condition was primary.

The reports of Jentzer [4] and of Iseu [7] are the best available ones regarding osteomyelitis of the pubis. Other reports of lesser value are those of Painter,[8] Chauvin,[9] McWhorter,[10] Klemm and Gayet.[11]

Jentzer was able to gather reports of 16 cases of chronic osteomyelitis in the literature up to 1934 (André, 2 cases; Painter, 3; Chauvin, 1; Marion, 1; Legueu, 2; Maisonnet, 2; McWhorter, 1; Söderlund, 1; Gayet, 2; Klemm, 1). His report discussed principally the vesical complications. He mentioned reports of cases of acute osteomyelitis reported by Lévi, Painter, Lagos Cjarcia and Armando, Ingelrans, Zaffagnini, and Cajaccini.

Iseu was able to find 25 cases of acute osteomyelitis, presumably of the hematogenous variety, also up to 1934. Undoubtedly these two series overlap. Iseu discussed all phases of the subject.

Painter reported 3 cases, in 1 of which the condition was due to the staphylococcus, and in 2 of which it was due to the streptococcus.

In McWhorter's case the pathologic condition began as pharyngitis and acute otitis and was followed by acute osteomyelitis of the clavicle, the tibia and the pubis.

Söderlund's report included 3 cases of hematogenous and 1 case of extensional osteomyelitis. He made the statement that the hematogenous condition is never associated with sinuses which communicate with the vaginal tract. The presence of the latter, in Söderlund's opinion, indi-

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7. Iseu, G.: Chir. d. org. di movimento **19**:1, 1934.

8. Painter, C. F.: Osteomyelitis of the Innominate Bone: Reasons for Rarity of Location; Methods of Repair, Operative and Otherwise, J. A. M. A. **86**: 341 (Jan. 30) 1926.

9. Chauvin: J. d'urol. **26**:548, 1928.

10. McWhorter, G. L.: Surg., Gynec. & Obst. **49**:205, 1929.

11. Gayet, in discussion on Chauvin.[9]

cates the history of a difficult labor, a tear in the vaginal mucosa and an extension of infection from the vaginal mucosa to the bone.

Osteomyelitis of the pubis is likely to be one of several lesions in the same person. In most cases the course is subacute, and in many cases a latent infection is present which comes to light only because of the occurrence of some complicating factor (see section on vesical complications). There are repeated exacerbations of pain and disability, with swelling anteriorly over the body of the pubis, along the superior ramus or on the fold of the perineum, where it passes into the inner side of the thigh corresponding to the descending ramus of the pubis.

During any period of acute exacerbation the pain, disability and swelling become more prominent. Disability is due principally to muscle spasm. External tenderness is present over the involved part of the bone. Rectal examination and, in women, vaginal examination yield information concerning any manifestations which point toward the pelvic cavity.

Marked swelling is always due to an abscess. The swelling may be located externally or may be situated internally in the pelvic cavity, where it may be discovered only on rectal or vaginal examination. The swelling and induration of the tissues may be located anteriorly around the neck and anterior surface of the bladder between the latter and the posterior surface of the pubis and are felt above the pubis by pelvic examination.

In many cases the entire clinical picture, the manifestations of the illness and the end result, is directly produced by the local complications of the osteomyelitis.

A. *Abscess Formations.*—Abscess formations occur almost invariably. According to the situation of the osteolytic focus, the abscess may be situated in either sex: (*a*) between the bladder and the posterior surface of the body of the pubis and the ascending ramus, that is, in the space of Retzius; (*b*) externally over the anterior surface of the body and ascending ramus of the pubis, spreading under the skin of the lower part of the abdomen and of the anterior surface of the hip and thigh; (*c*) externally over the external surface of the descending ramus of the pubis, spreading down in the fold of the perineum and down along the inner side of the thigh. In addition, in the male patient an abscess originating from a focus on the posterior aspect of the descending ramus of the pubis may take the anatomic position of an ischiorectal abscess. An extension from an abscess in some neighboring situation may also appear in the ischiorectal fossa. In women, an abscess may form (*a*) from the inner margin of the descending ramus, spreading along the lateral wall of the vagina or (*b*) from the posterior aspect of the pubis and its descending ramus, spreading along the lateral wall of the vagina and extending up toward and into the rectovaginal septum and the ischiorectal fossas.

B. *Vesical Complications.*[12]—In many cases of osteomyelitis of the pubis, even in those without original or associated trauma, vesical symptoms and complications occur. The biologic development of the vesical complications is as follows:

(*a*) Pyuria: Pyuria occurs as a single objective symptom, and when persistent it should call attention to the possible development of the following clinical progression.

(*b*) Perforation of the Bladder: Reports in the literature of perforation of the bladder from abscesses associated with osteomyelitis of the pelvis are not common. De la Peña [13] in 1931 was able to find only 5 cases and added 1 of his own. In a discussion of Chauvin's [9] paper before the French Society of Urology in November 1928 Maisonnet mentioned 2 cases, Marion 1 and André 1 (referred to previously). All the cases except André's were observed during the World War and were associated with injury to the pubic bone. This brings the total up to 10 cases, according to Hepler and Eikenbary.[14]

From their observation of 4 cases of severe chronic osteomyelitis of the pelvis in children Hepler and Eikenbary stated the opinion that this complication is often imminent in cases of suppurative lesions of the pelvic bones. This statement is based on the finding in all 4 of their cases of a definite displacement of the bladder and in 2 of the cases of perforation of the bladder by sequestrums with the formation of osteovesical fistulas. They assumed that perforation was impending in the other 2 cases because of the existence of the same engendering factors present in the 2 with perforation.

In the cases of Hepler and Eikenbary the displacement of the bladder was caused by a massive involucrum and not by a pelvic abscess. In each of the 2 cases with perforation the sequestrum plugged the opening of the osteovesical fistula. In 1 the opening was in the lateral aspect of the basal zone, and in the other it was in the fundal zone. In both the side of the bladder involved was firmly adherent to the involucrum, with a large amount of fungoid or granulomatous tissue between the bones and the bladder. The bladder wall at the point of perforation was so firmly adherent to the involucrum that there was no extravasation or urinary leakage. Nor was there any evidence of the previous existence of the conditions.

(*c*) Vesical Fistula: Under such conditions the further development of the complication leads to the formation of the osteovesical

12. It is most convenient to discuss the subject of vesical complications of osteomyelitis of the pubis here without regard to the type or character of the osteomyelitis or its originating or associated causative factors.

13. de la Peña, A.: J. Urol. **26**:473, 1931.

14. Hepler, A. B., and Eikenbary, C. F.: Am. J. Surg. **22**:113, 1933.

fistula. A fistula commonly extends from the bladder to the focal area in the bone or to the skin or communicates with the vagina or the rectum.

(*d*) Vesical Calculi: The next step is usually the formation of calculi, and, as in some of the reported cases, sequestrums are found to form the nuclei of the bladder stones. The calculi are apt to reform continuously until the vesical fistulas are closed and the osseous lesion is in a healing stage or is solidly healed.

In Marion's case the condition followed a bullet wound in the pubic region. There were no symptoms for two years; then there were marked vesical symptoms. Cystotomy was done, and a calculus was found. In the middle of the calculus a sequestrum was discovered. There was a recurrence of symptoms ten months later, when osteomyelitis of the pubis was demonstrated roentgenologically. A second calculus was found in the bladder and was removed. Permanent healing occurred thereafter.

Legueu [15] observed 2 cases of war wounds with vesical symptoms and vesical fistulas. There was recurrent calculus formation. Healing of the fistulas took place after curettage of the sinuses and the bone. Nevertheless, there were many subsequent recurrences of the bladder stones.

Clinical Progression.—In some of the reported cases (Hepler and Eikenbary [14]) there were no subjective signs of vesical complication. This accounts for the failure to consider the possibility of this complication. Even in cases in which perforation is present, there may be no subjective symptoms. In a good many cases persistent pyuria was the first indication of the vesical complication.

In the others, the symptoms in the beginning are those of irritation of the bladder: frequent urination, pain, hematuria and pyuria. The vesical symptoms are commonly so prominent as to dominate the clinical picture and cause most of the symptoms. Under comparable conditions one should always think of the possibility of osteomyelitis of the pelvis (pubis), and one should not be misled by the apparent dominance of the urologic symptoms.

The presence of an apparently persistent fistula in the general neighborhood of the bladder should awaken similar suspicions and lead to similar investigations to prove or disprove the presence of osteomyelitis in the adjacent bone.

The same is true of the demonstration of vesical calculi. The repeated formation of stones should also point to the possibility of the presence of osteomyelitis.

Cystoscopic and roentgenologic examination should be employed as a routine in all these contingencies. When adequate information of this kind is available the diagnosis should not be difficult.

The operation for the cure of an osteovesical fistula is sometimes difficult because of the firm adhesions of the contiguous portion of the bladder to the involucrum and because of the infiltration about the

15. Legueu, F., in discussion on Chauvin.[9]

fistula; a frequent complication is more or less extensive laceration of the bladder. Healing is rapid, and the operative results are good. Once corrected, the condition does not tend to recur provided the osteomyelitis is adequately controlled.

VI. OSTEOMYELITIS OF THE ISCHIUM

Cases of osteomyelitis of the ischium fall into three groups:

1. Cases in which the condition is limited to the acetabular portion (body) of the ischium. These have already been described (see section on osteomyelitis of the acetabular portion of the innominate bone).

2. Cases in which osteomyelitis appears in the ascending ramus of the ischium. These are similar in all particulars to cases of osteomyelitis in the descending ramus of the pubis, and the differentiation can be made only roentgenologically. In some cases both the ischium and the pubis are involved, either simultaneously or consecutively by extension of the process. When the process is limited to the ischium, vesical complications are not likely to occur.

3. Cases in which there is osteomyelitis of the descending ramus and tuberosity of the ischium. It is almost impossible to differentiate clinically between these various areas except by roentgenologic means and by the facility with which foci in the descending rami spread into the body and then into the hip joint. According to McWhorter, the clinical picture and the roentgenologic evidences of this extension of the disease to the hip resemble very closely the picture of the type of acute nonsuppurative ankylosing arthritis described by Stern.

The general symptoms are similar to those in the cases in the other anatomically distinguished groups. The local symptoms are more or less similar also: pain, deformity, muscle spasm, swelling, limitation of motion and postural deformity. Tenderness is present over the involved part of the bone and is apt to be located medially and toward the posterior aspect. The physician has only the points of tenderness, the roentgenologic findings and the characteristic distribution of abscesses to enable him to attempt to make anatomic differentiations. As the ischium is situated medially and posteriorly to the hip and thigh, abscesses originating from the external, extrapelvic aspects of the bone are apt to be present on the posterior medial aspect of the thigh, beginning as collections of pus in the lowermost depths of the buttock and then spreading in a downward direction. Those which originate on the pelvic aspects of the ischium and point inward form the majority of the pelvic and ischiorectal abscesses which appear in association with osteomyelitis of the pelvic bones. For this reason rectal and vaginal examinations are important.

ROENTGENOLOGIC ASPECTS OF OSTEOMYELITIS OF THE PELVIC GIRDLE

In discussing the various phases of this subject many roentgenologic facts have been alluded to and described. These it is not necessary to repeat.

In the general consideration of roentgenologic facts relating to osseous tissue it must be remembered that lesions of the bone take a long time to develop sufficiently to produce differentiating shadows on the roentgenogram. When the periosteal layers are fully developed and can be clearly visualized in the pictures, the first signs of change are linear differentiations of the periosteum, which grow thicker as involucrum is deposited. As a general rule it takes from eight to ten days for these changes to become perceptible. The next changes occur in the osseous tissue and vary, in accordance with the length of time interposed from the beginning of the pathologic process, from smaller and larger areas of rarefaction to areas of necrosis and to completely differentiated and separated sequestrums of various sizes and shapes. In the thin plates of the iliums perforations are common. In the late stages the effects of destruction of osseous tissue are easily visible both in the amount of tissue destroyed and in the compensating morphologic changes of the remaining segments, as well as in the amount of involucrum which is formed. Comparison of the two sides of the pelvic girdle commonly give striking effects.

Tilting of the pelvis is evident in the roentgenograms. The shadows of the rami of the pubis and ischium overlap on the affected side, so that it is often necessary to retake the picture with the x-ray tube farther down in order to show the obturator foramen and the rami.

With proper technic in tilting the pelvis abscesses in the pelvic cavity can frequently be visualized in the films; and when the abscesses are beyond the reach of the finger the x-ray apparatus is an invaluable aid in demonstrating them.

In cases in which fistulas are present a roentgenogram taken after injection of the sinuses with a radiopaque solution will commonly indicate the origin of the suppuration.

The differential roentgenologic diagnosis is usually not difficult. Occasionally when the condition complicates a malignant lesion (see section on osteomyelitis following suprapubic cystotomy) care is necessary in distinguishing between the neoplastic and the inflammatory changes. The experienced roentgenologist should, however, have no difficulty in making the differentiation both under ordinary and under extraordinary conditions.

In all cases of suppurative lesions about the pelvis, of recurring lesions of this type about the pelvis or of similar lesions which do not heal after drainage, a causative focus in the bones of the pelvic girdle should be sought roentgenologically.

For emphasis, attention is again called to the relation of vesical calculi to sequestrums and inflammatory lesions about the bladder and the pubis, and to the importance of roentgenologic study as a means of ordinary and differential diagnosis (see section on vesical complications of osteomyelitis of the pubis).

TREATMENT OF OSTEOMYELITIS OF THE BONES OF THE PELVIC GIRDLE

Throughout this communication the general principles governing the treatment of the lesions have been indicated. It will be readily seen and appreciated that the treatment of osteomyelitis falls into two categories:

1. In treating osteomyelitis of the first type the physician is compelled by the anatomic situation of the lesion, by difficulties in diagnosis or by other equally important factors to assume a conservative attitude, and operation, even the simple incision of a frank abscess, must necessarily be done at an advanced stage of development of the lesion. Curiously, clinically it is found that the mortality either is not materially different or is less than when the condition is treated surgically.

2. For osteomyelitis of the second type surgical treatment of some kind is given. An analysis of these forms of treatment follows:

(*a*) Simple incision and drainage of abscesses are done.

(*b*) Unaided casting off of sequestrums is observed during the course of healing of the resulting sinuses; or occasionally this is aided by operative means.

(*c*) In certain situations and under exceptionally favorable conditions osteotomies of various kinds are done. In the ilium these are usually more successful than in other locations, because the anatomic conditions are favorable.

(*d*) Complications arise, such as vesical complications or occasionally spinal complications, which necessitate surgical treatment because of themselves rather than because of the osseous infection. Final success is always directly proportionate to the extent to which the bone lesion is susceptible to proper eradication and drainage.

(*e*) Because of any or all of these reasons, sinuses and fistulas constantly develop, persist and show little evidence of permanent closure, and "revisions" of the apparent condition are constantly repeated. For this reason a belief in the hopelessness of any surgical intervention for these seemingly intractable lesions has become rooted among physicians.

It becomes apparent that except when complications (such as bladder complications) compel surgical therapy, the entire field of endeavor has consisted and still consists in incision and drainage of abscesses and repeated revisions of the resulting sinuses.

Abscesses superficial to the pelvic bones are usually under observation as they develop. Abscesses representing exceptions to this rule exist in association with the ischium, which is buried in the depths of the musculature. All other abscesses fail to come under observation until they are relatively old. The surgical approach to the latter abscesses is usually difficult or dangerous or both, and for this reason drainage is usually accomplished where the abscess finds its way to the skin and points. A persistent sinus usually follows. In the treatment of an abscess of the pubis and the ischium an approach through the medial side of the thigh is recommended by McWhorter: The adductor muscles are split, and a large area is opened, which permits drainage of practically all parts of the pubis and the ischium.

Sufficiently radical surgical treatment is possible only in the flare of the ilium. The technical procedure is simple. The bone is exposed and bared on each side at the site of the lesion by and through an appropriately placed incision. It is possible to resect the entire area of the lesion. Adequate drainage of any subperiosteal abscess should be provided. Frequently it is possible to do a secondary suture of the wound with a consequent material shortening of the period of invalidism.

In all other parts of the pelvic girdle radical operation has been considered difficult, not wise because of anatomic and physiologic difficulties or too dangerous to life; and not many surgeons have been sufficiently courageous to overcome these obstacles repeatedly. It must be confessed that this attitude is a wholesome one and is to be encouraged, as the practical aspects of the problem fit in with the best theoretic considerations regarding the correct and most advantageous method of treatment for osteomyelitis and refraining from intervention is the best that one can do at the present time in most of the cases.

The situation as regards therapy is best illustrated by the possibilities present in the treatment of lesions about the sacroiliac region.

Up to the time of Kulowski's report the treatment of osteomyelitis of the sacroiliac region was insufficient and unsuccessful. Surgeons have always considered suppurative lesions of this type originating in this region to be chronic conditions which are difficult and frequently impossible to heal. As a rule, drainage of the complicating intrapelvic or extrapelvic abscesses which usually occur has been the only treatment; and this treatment was recognized as being purely palliative. In hospital practice it was (and still is) not uncommon to have patients admitted for the incision and drainage of abscesses in the general sacroiliac region and then to have them readmitted periodically for revisions of the sinuses or for the incision and drainage of recurrent abscesses. No actual cure was ever obtained, and after a while such lesions were frequently thought to be extraordinary infections even when tubercle bacilli could not be found and other evidences of infection by specific organisms could not be proved.

It seems strange that surgeons did not attribute their uniform failure in the treatment of such a lesion to erroneous conceptions of the essential character of the process and to the insufficiency of their operations, although radical resection for tuberculosis was adequately described more than thirty years ago. The apparent neglect of similar treatment for the ordinary forms of osteomyelitis is understandable only because of the peculiar deep location of the lesions and the anatomic relations of the parts and because of the timidity of the surgeon toward operative attack in this region.

Bardenheuer [16] in 1899 was the first to urge radical resection of the sacroiliac joint for tuberculous involvement. The approach is made posteriorly through a modified Sprengle type of incision. The posterior half of the ilium is stripped subperiosteally on both the intrapelvic and the extrapelvic aspect, the sciatic notch being exposed. The ilium is sectioned vertically with a Gigli saw, which is passed through the lateral border of the greater sciatic notch. The mortality reported by Bardenheuer in 20 cases was 30 per cent. Schede since 1875 had done 26 such resections, with a mortality of 40 per cent and with 10 cures.

Painter [8] in 1908 reported 1 case in which the result of resection was fatal. The patient was in a desperate condition owing to tuberculous involvement of the entire region, and the operation was attempted as a last resort. Nevertheless, this apparently discouraged the further development of the procedure in this country.

Picque [17] in 1909 discussed total and partial sacroiliac resection for tuberculous osteomyelitis of the sacroiliac joint. His technic is a modification of that of Bardenheuer.

Kulowski's paper seems to be the first report of cases in which radical operations of this type have been deliberately undertaken for the cure of this form of chronic osteomyelitis. It goes without saying that the patient must be able to withstand a surgical operation. Preoperative general hygiene, blood transfusions and even preliminary drainage of the soft tissue are indicated when the patient is considered unfit to be operated on. Fluids containing dextrose and salt may be given subcutaneously with advantage preceding, during and after the operation. The general clinical situation, and not roentgenograms alone, should determine the immediate indication. Operations of this radical nature should not be done in the acute stage of the disease, and the management of the condition should be left as much as possible to nature, surgical intervention being the last resort.

Briefly, the technic of the operation of Bardenheuer as modified by Picque is as follows: The incision follows the line of origin of the

16. Bardenheuer, S., cited by Krecke: Centralbl. f. Chir. **26**:1329, 1899.
17. Picque: Bull. et mém. Soc. de chir. de Paris **35**:1107, 1909.

gluteus maximus muscle and is sufficiently large to give plenty of room for the manipulations. The ilium is bared, and the bone is stripped of its periosteum on both sides as far as the great sacrosciatic notch and as far as the superior and inferior posterior spines. The line of section of the iliac flare is determined by the extent of the disease, and the section is best made with a power saw or with a Gigli saw. In the radical operation the margin of the sciatic notch is removed. The flap of ilium so defined is levered out, and the sacrum is exposed. Removal of the diseased parts in the sacrum is done carefully with chisel, mallet and curet. When the débridement is complete the resultant wound is packed wide open, a generous dressing is provided and the entire pelvis is adequately immobilized in plaster. Healing occurs by granulation and is tedious. In suitable cases, however, an attempt may be made to hasten the cicatrization by secondary suture. When this is not possible, I agree with Kulowski that the wound is ideal for the Orr method of treatment. As a matter of fact, because of the situation and nature of the wound one is compelled to adopt this method.

During the course of the operation both external and pelvic abscesses will probably be encountered. Every pocket must be thoroughly and widely opened, and sufficient bone must be removed to make the final cavity regular in shape and mechanically healable. The danger of injuring the rectosigmoid is remote, and injury to the pelvic portion of the ureter is perhaps more likely; both of these possibilities should be kept in mind. If the sacral canal is opened or if the débridement encroaches on the sacral foramens the danger of destruction of the sacral nerves is imminent. Fortunately, loss of function of any of these nerves is not nearly as serious as is destruction of the spinal nerves higher up.

The danger of uncontrollable hemorrhage is constantly present. Care must be taken at the sciatic notch to avoid injury to the superior gluteal artery and vein; several fatalities have been reported from this cause. Bleeding from the bone and from numerous small vessels in the soft parts is frequently troublesome. Shock is also a factor to be reckoned with because of the extent of the operation and is usually present in proportion to the amount of blood lost. Intravenous infusions of dextrose solution and transfusions of blood are frequently needed to combat the loss of blood and the resultant shock and collapse.

The chief feature of the procedure is to adapt the amount of resection to the extent of destruction present. The operation is entirely clinical, and one works carefully from the surface to the depths until a healthy firm bed of bone remains. This is the ideal attainment even though the sacral canal is opened. Except when the operation is in experienced hands this will probably not be attained, principally because of the timidity of the operator. This defect, however, ought readily to be remediable.

The only contraindications to the total operation are present in young women who might bear children, in the very young and in general in patients whose physical condition is unfit to withstand any surgical treatment.

In addition, Smith-Petersen [18] in 1917 stated that this resection was too radical in any case except one in which the condition is extensive. He described his own ingenious lateral approach to the sacroiliac joint, in which a window is chiseled into the joint through the ilium. However, the primary surgical objective of the removal of diseased tissue, adequate drainage and subsequent immobilization, is not as thoroughly attained in the Smith-Petersen operation as in the operation of Bardenheuer and Picque.

Kulowski [6] recognized the validity of some of these criticisms and for this reason has modified his procedure in cases presenting these difficulties, performing an incomplete operation the essential feature of which is incomplete removal of the iliac flare. Essentially this means retention of the margin of the sciatic notch and a much less radical operation. In suitable cases one might do a partial primary operation and complete the procedure secondarily when the general condition of the patient and all other factors warrant it.

Visual and static deformity need not necessarily result from the complete operation. In Picque's 7 cases the ilium finally fused with the sacrum, as it did in 1 of the cases reported by Kulowski. The dense mass of soft tissue and the scar usually prevent any herniation.

In all cases immobilization of the pelvis is an important item in the treatment. In many cases the essential principles of the Orr method of treatment are followed to great advantage. This is true especially with lesions involving the sacroiliac region. The immobilization should always be adequate. For lesions surrounding the hip joint and in those involving the hip joint proper the treatment should include immobilization of the thigh either by plaster of paris or by weight extension and suspension. Care is to be taken that the final position of the limb is not disadvantageous.

MORTALITY

In the series reported by McWhorter, Raeschke, Doran and Brown and Lloyd there were 10 cases of osteomyelitis of the pelvic girdle, with 1 death—a mortality of 10 per cent. In the Mount Sinai series of 12 cases there were 2 fatalities—a mortality of approximately 16 per cent. The private patient to whom I referred also recovered. This indicates a general mortality of 12 per cent for all forms of osteomyelitis of the various bones of the skeleton.

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18. Smith-Petersen, M. N.: Am. J. Orthop. Surg. **15**:593, 1917.

STUDIES OF HEPATIC FUNCTION BY THE QUICK HIPPURIC ACID TEST

I. BILIARY AND HEPATIC DISEASE

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When Pierson, cited by Robertson and his associates,[1] said some years ago that perhaps the greatest good that had come out of the search for adequate tests of hepatic function was the awakening of interest in the state of the liver, he probably did not himself realize how important his statement was, even though he went on to say that in this regard most physicians "have been asleep in Zion and are in need of a great revival." On all sides today are signs, though in some quarters they are faint indeed, of the beginning of that revival. Just as the patient with deficiencies of the cardiac, renal and respiratory apparatus has long been considered a poor operative risk, so is the patient with hepatic deficiency or insufficiency coming to be considered an equally poor, if not a poorer, risk.

Our own interest in the problem was first aroused by our study of the "liver death" or "liver-kidney syndrome" occurring in operations on the biliary tract, to which for the last several years we have devoted considerable time and attention. In our search for some method of determining the type of case in which this catastrophe is likely to occur we came to realize two important things about the liver: that its surgical role is by no means confined to disease of the biliary tract and that at least part of the problem would be solved if some adequate test of its function could be discovered.

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The studies reported in the three papers in this series have been made under the direction of Dr. Urban Maes, Director of the Department of Surgery in the School of Medicine of Louisiana State University. The technical studies have been made by Ruth Mayne, B.S. in Med. Tech., R.T. Members of the staff of Louisiana State University in Charity Hospital cooperated with us, as well as members of the staffs of the Tulane University and Independent Units, who furnished us with many cases.

1. Robertson, W. E.; Swalm, W. A., and Konzelmann, F. W.: Functional Capacity of the Liver: Comparative Merits of Five Most Popular Tests, J. A. M. A. **99**:2071 (Dec. 17) 1932.

FUNCTIONS OF THE LIVER

Much of the present knowledge concerning the liver is due to the extensive clinical and experimental studies of Mann and his co-workers [2] at the Mayo Clinic. This organ, as Mann pointed out, is the servant of the body, as opposed to the pituitary gland, which is its master. From fetal life until life ends, the liver is a "physiological drudge," which constantly responds, often at the expense of its own cellular constituents, to the demands and needs of the rest of the organism. It has the ability to carry on many functions greatly in excess of normal needs, and it maintains those functions with extreme stubbornness, even when there is left only a small amount of normal functioning tissue with which to carry on. Indeed, Mann added, perhaps one of the reasons why the liver is so generally ignored is because of the efficiency with which it does its work under such adverse conditions.

The exact functions of the liver are still a matter of debate, and there is a rather general tendency to attribute to it any metabolic process which cannot be proved to take place elsewhere in the body. Disregarding that tendency, however, we are able to list certain of its functions which are fairly well established, even if they are not fully understood. These include:

1. The metabolism of carbohydrates. This function is possessed to some degree by all muscular structures, but the liver is the great storehouse of glycogen.

2. The metabolism of proteins. This function is not shared to an appreciable degree by any other structure, and the conversion to urea of the amino acids formed from proteins in the process of digestion seems to take place almost entirely in the liver.

3. The metabolism of bile. The bone marrow and the spleen share this function, but again the liver is the important organ. In it the bile acids, chiefly glycocholic and taurocholic acids, which are essential in the digestion of fats, are secreted in the form of salts.

4. The coagulation of the blood. The knowledge of the exact mechanism of this process is still confused, but the modern tendency, as the important studies of Quick, Stanley-Brown and others [3] have shown, is to attribute a large part of the task to the liver. At least indirect evidence of this function is furnished in cases of hepatic injury, in which the prothrombin in the blood plasma is diminished.

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2. Mann, F. C.: Hepatic Physiology and Pathology from the Surgical Viewpoint, Minnesota Med. **19**:695, 1936; Hepatic Function in Relation to Hepatic Pathology: Experimental Observations, Ann. Int. Med. **8**:432, 1934.

3. Quick, A. J.; Stanley-Brown, M., and Bancroft, F. W.: Study of the Coagulation Defect in Hemophilia and in Jaundice, Am. J. M. Sc. **190**:501, 1935.

5. The detoxification of poisons, bacteria and other harmful substances. This special function, again, is apparently shared with no other structure to any similar degree.

6. The thermogenic function. Crile,[4] who is chiefly responsible for the emphasis now placed on this function, has shown that the liver produces approximately a third of the heat of the entire organism and that the introduction of heat within the abdomen causes a synchronous rise in the temperature of the liver and the brain.

7. The power of regeneration, which is sometimes described as one of the functions of the liver, must be constantly borne in mind, for it explains much that on the surface is confusing and contradictory. The Mayo Clinic studies have demonstrated that even when as much as 80 per cent of the liver substance is removed complete regeneration of the excised area occurs in six to eight months. They have also demonstrated that a relatively small amount of normal tissue is necessary for normal function. This explains why tests of hepatic function may give negative results even in the presence of such conditions as hepatic malignant tumor and hepatic cirrhosis as long as they remain localized, or, more exactly, as long as they do not involve the entire hepatic structure. It also explains why the mere existence of jaundice or the mere enlargement of the liver noted in various pathologic states does not necessarily bring about the condition loosely termed "liver insufficiency." [5]

The concomitance of pathologic changes in the liver and disease of the biliary tract was first noted by Reimann [6] in 1917 and by Graham,[7] who adduced both clinical and experimental proof, in 1918. Their work has been repeatedly corroborated, Flint's [8] studies being especially important. He was able to show two things: that even macroscopically normal livers frequently reveal microscopic damage under such circumstances, and also (a fact of which we shall make considerable use in a later paper) that hepatitis is a rather frequent finding in nonbiliary disease even though no hepatic damage has been suspected.

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4. Crile, G. W.: Function of the Liver in Relation to Operation on Gallbladder and Ducts, J. A. M. A. **87**:309 (July 31) 1926.

5. Helwig, F., and Schutz, C. B.: A Liver Kidney Syndrome, Surg., Gynec. & Obst. **55**:570, 1932. Boyce, F. F., and McFetridge, E. M.: So-Called "Liver Death": A Clinical and Experimental Study, Arch. Surg. **31**:105 (July) 1935; "Liver Deaths" in Surgery: An Analysis of Thirty-Four Cases, New Orleans M. & S. J. **88**:563, 1936; The So-Called "Liver Death": An Experimental Study of Changes in the Biliary Ducts Following Decompression of the Obstructed Biliary Tree, Arch. Surg. **32**:1080 (June) 1936.

6. Reimann, S. P.: Cholesterol Content of Blood in Gallstone Disease, Surg., Gynec. & Obst. **26**:282, 1918.

7. Graham, E. A.; Cole, W. H.; Copher, G. H., and Moore, S.: Diseases of the Gall-Bladder and Bile Ducts, Philadelphia, Lea & Febiger, 1928.

8. Flint, E. R.: Association Between Gall-Bladder Lesions and Hepatitis in Human Subjects, Brit. M. J. **1**:1041, 1930.

Judd [9] has suggested that the hepatitis which is often found at operation and which has given rise to no clinical manifestations may furnish, per se, actual evidence of the detoxifying activity of the liver. Bacteria, he noted, are only rarely demonstrated in such livers, but the gross findings are characteristic. The liver is enlarged; the tissue is firmer than normal; and the surface reveals many whitish lines. The edge of the liver may terminate sharply in such a whitish line or may be rounded and edematous. Heyd [10] joined Judd in stressing the importance of routine inspection or palpation of the liver at all operations. He concluded that persons with small and atrophic livers are likely to respond poorly to surgical treatment, the response being in some way proportionate to the reduced size of the liver, and that such persons should be protected against possible postoperative hepatic complications before these have a chance to develop.

TESTS OF HEPATIC FUNCTION

At the present time most tests of hepatic function are highly unsatisfactory until the disease is so far advanced that the information which they supply is no longer necessary. They are of the same degree of crudeness, Graham [11] stated, as Richard Bright's test of renal function, which was performed by boiling urine over a spirit lamp. Certain things, however, may be said in their defense. In the first place, too much has been demanded of the individual test. Because of the wide variety of known hepatic functions, no one test can possibly be expected to reveal everything about the liver, and no single test should be relied on or condemned from so unreasonable a standpoint.

In the second place, no test of any sort takes the place of scientific knowledge, clinical experience and diagnostic acumen. Tests are of value only in proportion to the knowledge and wisdom of the physician who uses them. They may furnish additional facts, confirm a clinical diagnosis, less often establish it, indicate the risk of operation, suggest corrective preoperative therapy and point out the need of postoperative treatment, but more than this they cannot do, nor should more be expected of them. The chief and final responsibility remains the surgeon's.

In the third place, even repeated tests cannot be relied on implicitly, and a single test, we are inclined to say, should not be relied on at all. It is not inconceivable, as we have already implied, that the patient's

9. Judd, E. S.: Physiology of the Liver and Its Relation to Surgery of the Biliary Tract, Ann. Surg. **90**:1035, 1929.

10. Heyd, C. G.: The Chemical Mechanism of Liver Protection in Abdominal Surgery, Tr. Am. A. Obst. **46**:102-107, 1933.

11. Graham, E. A.: Estimating the Risk of Operations on the Biliary Tract by Testing the Excretory Function of the Liver, Radiology **21**:191, 1933.

state may be extremely grave while his hepatic function remains within normal limits as one is able to measure those limits. In other words, the most accurate of tests must be permitted a reasonable margin of error, and it is possible, because of the enormous reserve capacity of the liver, for a number of things to be seriously wrong while hepatic function remains unimpaired, at least by available standards of measurement.

Finally, it is impossible to employ the theoretically excellent precaution of performing every test on every patient, particularly when the tests involve (as so many of them do) repeated venous punctures. Quite aside from the time and expense inherent in such a plan, the average patient, as Robertson said, has decided objections to "being his own guinea pig." Even if he would tolerate it, there is a more fundamental objection. The type of patient who is most likely to be benefited by the information derived from multiple tests is also the type of patient who should not be submitted to miscellaneous venous punctures. Valuable as the information thus obtained may prove to be, it is by no means as valuable as the preservation of intact veins for the introduction of fluids which later may save life.

Mann laid down certain other requirements for tests of hepatic function which involve the use of extraneous substances. Before such agents are employed, he said, two things must be clearly demonstrated: that the liver destroys all, or at least a major portion, of the substance chosen, and that the direct or indirect quantitation of the substance is possible after it has passed through the liver. He added, rather caustically, that the sponsors of most tests previously proposed have seldom troubled themselves to meet these specifications. He added another warning, that the outcome of any test is likely to vary according to whether it is performed on a glycogen-empty or on a glycogen-filled liver. Our own results with the Quick hippuric acid test of hepatic function have demonstrated the importance of this consideration. It is also demonstrated by the recent experimental work of C. S. Stone (cited by Lehman [12]), on which we shall comment later, and by the work of Forsgen and Gerritzen,[13] which suggested a definite rhythm in hepatic function.

Before proceeding to a consideration of the Quick test it is necessary to discuss the various tests of liver function which have previously been proposed. Such tests may be roughly classified under the headings of the various functions of the liver which they are supposed to illuminate,

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12. Lehman, E. P., in discussion on Payne, R. L.: Postoperative Care in Surgery of the Bile Tract, J. A. M. A. **109**:1436 (Oct. 30) 1937.

13. Gerritzen, F.: Liver Diuresis as Result of Rhythmic Function of Liver, Acta med. Scandinav. **89**:101, 1936; abstracted, J. A. M. A. **107**:754 (Aug. 29) 1936.

aside from a large group of miscellaneous and often entirely illogical tests, most of which we shall ignore.

Tests of carbohydrate function include typically the galactose test [14] and the levulose tolerance test. Both are based on the theory that in persons with hepatic dysfunction the rate of utilization of a predetermined amount of carbohydrate will be slower than in normal persons, and therefore a greater amount of the substance will persist in the general circulation and be excreted in the urine. The galactose tolerance test is generally regarded as unreliable. Jones,[15] for instance, found its results normal in 2 cases of acute yellow atrophy, in both of which the diagnosis was proved by postmortem examination, and many other observers have had equally unsatisfactory results with it. Mann's conclusion was that too many factors are involved in the mechanism of sugar metabolism to make the test at all reliable, aside from the fact that there is a wide variation in the rate of utilization of dextrose by normal subjects.

The levulose tolerance test, while somewhat more accurate, is open to similar objections. Mann pointed out that the theory on which it is based is defective, in that the muscles as well as the liver make glycogen from levulose. His experiments performed in association with Bollman,[16] furthermore, have demonstrated that a hepatectomized animal is capable of utilizing levulose. Flint, who found the test fairly accurate on the basis of a comparative histologic study of liver tissues, defended it on the ground that hepatic insufficiency can exist without clinical evidence; this defense, however, as we have pointed out, holds for all tests.

Studies on nitrogen partition have proved of no particular value, because extremely severe hepatic damage is apparently necessary to cause any significant alteration in these values. Studies of the urea, ammonia, amino acid, nonprotein nitrogen and uric acid contents of the blood have been made by competent observers, many of them by Mann and Bollman at the Mayo Clinic, with such varying and generally disappointing results that their independent value is practically nil. If they are employed at all, they should be considered purely of auxiliary value and should never be relied on for therapeutic or prognostic direction.

Tests of bile metabolism include typically the icteric index test, the van den Bergh test, the Fouchet test, the urobilinogen test, the test for bilirubinuria and the bilirubin test. The icteric index test is, as its name implies, a test for jaundice. It is a simple, reasonably accurate test, the

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14. Jankelson, I. R., and Lerner, H. H.: Intravenous Galactose Liver Function Test, Am. J. Digest. Dis. & Nutrition **1**:310, 1934.

15. Jones, C. M.: The Treatment of Acute Hepatic Insufficiency and Its Relation to Prognosis, Am. J. Digest. Dis. & Nutrition **3**:624, 1936.

16. Bollman, J. L., and Mann, F. C.: Experimentally Produced Lesions of the Liver, Ann. Int. Med. **5**:699, 1931.

chief value of which is in the revelation of latent or subclinical jaundice and in the demonstration of fluctuations in the icterus which cannot be detected by simple clinical observation. Its weakness lies in a consideration which we have already commented on, that the mere existence of jaundice does not necessarily imply a deficiency of hepatic function.

The van den Bergh test is a qualitative and quantitative estimate of the content of the bile pigment in the blood, based on the Ehrlich diazo reaction. It furnishes much the same information as does the simpler icteric index test, and it is open to such possibilities of misinterpretation that many observers are unwilling to use it at all as a test of liver function. The Fouchet test falls into the same category.

The urobilinogen test [17] is based on the fact that urobilin produced in the intestinal tract is converted to bilirubin in the liver, completely if hepatic function is normal, incompletely if it is not (in which case it spills over into the urine as urobilinogen). Opinions vary widely as to the value of the test. Robertson stated that it merits little consideration. Elman and McMaster, as well as Pierson, in a discussion of Robertson's paper, stated that in their opinion it is the most delicate single test available for an estimate of liver dysfunction. It has the advantage of simplicity of performance, though there is disagreement as to how it should be interpreted. If no urobilinogen is present in the specimen it may be assumed that biliary obstruction is complete. If it is present in dilutions greater than 1 in 20, it may be assumed that hepatic damage is extensive. Killian in the discussion previously referred to pointed out that the rate of excretion varies at different periods of the day, as well as from day to day, in cases of catarrhal jaundice and allied conditions. In his opinion the test should be a twenty-four hour one, and the result should not be considered negative unless the negative reaction persists for five consecutive days. Five days, however, is a rather long period to wait for information about a seriously ill patient.

The presence of bilirubin in the urine as demonstrated by the bilirubinuria test is predicated on the presence of an excessive amount of bilirubin in the blood stream. The test is simple and is of undoubted value in conjunction with other tests. Few, however, would be inclined to be as positive as Leveruf and Berceanu (quoted by Graham), who stated that by its application the diagnosis of gallstone colic can be made within a few hours after the onset of symptoms and long before the appearance of jaundice.

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17. Piersol, G. M., and Rothman, M. M.: Practical Value of Liver Function Tests, J. A. M. A. **91**:1768 (Dec. 8) 1928. Greene, C. H.; McVicar, C. S.; Rowntree, L. G., and Walters, W.: Diseases of the Liver: III. Comparative Study of Certain Tests for Hepatic Function in Patients with Obstructive Jaundice, Arch. Int. Med. **36**:418 (Sept.) 1925.

The bilirubin test of von Bergmann and Eilbott [18] is undoubtedly a very sensitive test of hepatic function. Chemically pure bilirubin is introduced into the blood stream, and the amount in the plasma or serum is determined before the injection and also five minutes, three hours and four hours afterward, the amount recovered being interpreted as an index of the excretory function of the liver. The test has been greatly simplified since its introduction, but aside from the repeated venipunctures required the cost is prohibitive. Bilirubin costs approximately $25 per gram, which makes a single test expensive and repeated tests, which we consider necessary in all cases, beyond reason for public charges and almost impossible for all but the most affluent of private patients. The test also has the serious defect that it cannot be used in cases in which jaundice is present. Harrop and Barron [19] found that it frequently reveals unsuspected latent or subclinical jaundice; in their opinion, as in that of most observers, it is both accurate and delicate. Snell and Plunkett, on the other hand, were decidedly less enthusiastic.

Most excretory tests of hepatic function are based on the same principle, the injection of a dye into the blood stream and the determination of the degree of retention at stated periods thereafter. Various agents have been used for this purpose, but phentetiothalein sodium (phenoltetraiodophthalein sodium), which is now rather generally employed, is as satisfactory as any and, like the other halogen derivatives, has the additional advantage of making cholecystography possible at the same time.

The value of the dye test for hepatic function was discovered accidentally in Graham's [20] clinic, where its application has given brilliant results. In a study of 4 entirely unexpected "liver deaths" which occurred after operations on the biliary tract, it was found that all the patients had shown after cholecystography a high retention of dye, varying from 60 to 90 per cent. Later studies revealed that normal persons during the same period had a retention of only 10 to 15 per cent. The accidental finding was promptly turned to account, and since the method has been employed in Graham's clinic and no patient with a retention of more than 50 per cent of dye has been operated on without careful preparation, the mortality for cholecystectomy has been reduced from 6 per cent to 0.4 per cent and the mortality for operations on the common duct from 7.7 to 2 per cent.

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18. Jankelson, I. R., and Gargill, S. L.: Bilirubin Liver Function Test: I. Modification of the Method, New England J. Med. **20**:547, 1931.

19. Harrop, G. A., Jr., and Barron, E. S. G.: Excretion of Intravenously Injected Bilirubin as Test of Liver Function, J. Clin. Investigation **9**:577, 1931.

20. Graham, E. A.: Lowering the Mortality After Operations on the Biliary Tract, Illinois M. J. **60**:196, 1931.

Other observers have testified to the value of the dye test. Magath [21] reported that it indicates obstruction long before the patient exhibits jaundice. Greene [22] and his associates found it so constantly accurate in cases of portal cirrhosis that in the absence of positive findings they advised extreme caution in attributing ascites to a hepatic lesion. Greene also cited the finding of Chapman and his associates, that the average duration of life varies inversely with the degree of retention of dye. This would make the test valuable in determining the surgical risk versus the possible results of such operations for the relief of cirrhosis as the Talma-Morison omentopexy, splenectomy, and ligation of the coronary veins of the stomach. Greene and Conner [23] also considered the test valuable in determining the surgical risk of splenectomy and in demonstrating possible hepatic metastases from various types of malignant tumor. Bargen and his associates [24] have used it in this fashion in operations on the large bowel.

Lahey and his associates [25] have employed the test in several thousand cholecystectomies. They consider it very valuable but have warned against its use for patients with anginal and cardiac disease, emaciated patients, "poor risk" patients, jaundiced patients and patients with acute or subacute cholecystitis. For such subjects, Lahey stated, the introduction of the dye may cause an exacerbation of the disease which will require immediate operation. Obviously, these limitations materially reduce the usefulness of the test, for many such patients are included in the group of patients for whom information as to the state of hepatic function would be of extreme value.

The tests which we have mentioned are the principal tests of hepatic function in general use. Certain others less generally used must also be mentioned. Weiss [26] said that the lactic acid test is a useful prognostic aid in cases of jaundice, the elevation of the normal level (5.5 to 8.5) indicating a rapid destruction of glycogen in the liver and possible

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21. Magath, T. B.: The Takata-Ara Test of Liver Function, Am. J. Digest. Dis. & Nutrition **2**:713, 1935.

22. Greene, C. H.; McVicar, C. S.; Snell, A. M., and Rowntree, L. G.: Diseases of the Liver: VI. Comparative Study of Certain Tests for Hepatic Function in Cases of Cirrhosis of the Liver, Arch. Int. Med. **40**:159 (Aug.) 1927.

23. Greene, C. H., and Conner, H. M.: Diseases of the Liver: V. Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System, Arch. Int. Med. **38**:167 (Aug.) 1926.

24. Bargen, J. A., and Rankin, F. W.: Tests of Hepatic Function in Carcinoma: Their Value in Cases of Neoplasm of Colon With and Without Metastasis to Liver, Ann. Surg. **91**:225, 1930.

25. Lahey, F. H.: Present Management of Biliary Tract Disease, S. Clin. North America **12**:549, 1932. Clute, H. M.: Surgical Management of Obstructive Jaundice, ibid. **12**:565, 1932.

26. Weiss, S.: Liver Deaths and Their Prevention, Am. J. Surg. **23**:96, 1934.

impending toxemia. Epstein and Greenspan,[27] of Mount Sinai Hospital in New York, studied the cholesterol and the cholesterol ester content of the blood in cases of hepatic and biliary disease, finding the ester value markedly lowered in the presence of acute hepatic degeneration and inclined to be absent in cases in which the termination was rapidly fatal. The cholesterol values are less strikingly altered. In mild conditions the initial levels are only moderately depressed, and there is usually a prompt return to normal.

Determinations of serum albumin and globulin have been advocated by several authors. Foley and his associates [28] found that in the presence of advanced hepatic damage the albumin content of the serum is reduced and there is a reversal of the albumin-globulin ratio. Snell also found that both clinically and experimentally a rise in globulin and a fall in albumin indicate increasing hepatic damage, while the findings are reversed as improvement takes place. The Takata-Ara test, which was originally devised to differentiate meningitis from syphilitic involvement of the central nervous system, is also based on the ratio of albumin to globulin. It has the major defect, Magath pointed out, of being an empiric phenomenon and not yet explained on any satisfactory scientific basis. Its users report from 10 to 50 per cent of error, which is clearly too wide a margin for safety. Kirk,[29] who collected from the literature 3,583 cases in which it had been employed, concluded that its results are likely to be positive in any condition, hepatic or nonhepatic, in which the globulin level is elevated. Aside from its difficulty of performance, this makes it too insensitive to be used as a test of hepatic function.

Crandall, discussing the paper by Robertson and his associates to which we have referred several times, mentioned the test for blood lipase. Among 130 persons without hepatic disease he found only 6 with positive reactions for lipase, whereas the test yielded positive results in 80 per cent of patients with hepatic damage and in 100 per cent of experimental animals. It is not generally used.

Lichtman [30] in 1931 proposed a test for hepatic function based on the administration of a standard oral dose of cinchophen and a determination by colorimetric methods of the twenty-four hour excretion of oxycinchophen in the urine; excretion of more than 21 per cent of the

27. Epstein, E. Z., and Greenspan, E. B.: Clinical Significance of Cholesterol Partition of Blood Plasma in Hepatic and in Biliary Diseases, Arch. Int. Med. **58**:860 (Nov.) 1936.

28. Foley, E.; Keeton, R. W.; Kendrick, A. B., and Darling, D.: Alterations in Serum Proteins as an Index of Liver Failure, Proc. Soc. Exper. Biol. & Med. **33**:430, 1935.

29. Kirk, R. C.: The Takata-Ara Test and Its Relation to Cirrhosis of the Liver, J. A. M. A. **107**:1354 (Oct. 24) 1936.

30. Lichtman, S. S.: Cinchophen Oxidation Test of the Function of the Hepatic Cells, Arch. Int. Med. **48**:98 (July) 1931.

amount administered indicates hepatic dysfunction. The test seems to be very reliable. On the other hand, in view of Palmer, Woodall and Wang's [31] comprehensive study of cinchophen and toxic necrosis of the liver one would hesitate to administer this agent, even in nontoxic doses, to patients in whom hepatic dysfunction was suspected, especially since the test, to be of value, demands repetition.

It is clear that most of the tests which we have outlined are unsatisfactory. The simpler tests are inaccurate or insensitive, if not both. The more reliable tests are too complicated for general use, or too expensive, or not applicable to the type of patient for whom they would be most useful. Finally, as we have already noted, the majority of such tests require repeated venous punctures, the information from which rarely compensates for the damage done to veins into which it may later be urgently necessary to introduce life-saving fluids.

QUICK HIPPURIC ACID TEST OF LIVER FUNCTION

In our own search for a simple, safe, reasonably accurate test of hepatic function, our attention was drawn to the hippuric acid test, advocated by Quick [32] in 1932 and 1933. We have used it with increasing satisfaction for eighteen months, and have found that it possesses most of the advantages and is free from most of the disadvantages of the tests we have just listed. Before passing on to our own experiences with it, it may be of interest to outline the story of its development,[33] which is both curious and interesting.

The synthesis of hippuric acid was demonstrated by Wöhler in 1824. In 1877 Bunge and Schmeidenberg, in experiments long regarded as final, showed that hippuric acid was formed when the kidneys of dogs were perfused with benzoic acid and aminoacetic acid. They therefore concluded that the kidney was the site of the synthesis, and their observations were confirmed by Kochs in 1879 and by Cramer in 1902.

On the other hand, these experiments were not always accepted without question. In 1857 Kühne and Hallwachs had stated that the synthesis of hippuric acid might occur in the hepatic vessels in the presence of glycocholic acid. In 1911 Friedman and Tachau isolated hippuric acid after perfusing the liver of a rabbit with blood containing benzoic acid but no aminoacetic acid; they concluded that in this species

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31. Palmer, W. L.; Woodall, P. S., and Wang, K. C.: Cinchophen and Toxic Necrosis of Liver: Survey of Problem, Tr. A. Am. Physicians **51**:381, 1936.

32. Quick, A. J.: Conjugation of Benzoic Acid with Glycine, a Test of Liver Function, Proc. Soc. Exper. Biol. & Med. **29**:12, 1932; The Synthesis of Hippuric Acid, Am. J. M. Sc. **185**:630, 1933.

33. Hirscheimer, A.: Synthesis and Excretion of Hippuric Acid in Pregnancy, Am. J. Obst. & Gynec. **29**:395; 1935.

the synthesis might occur in the liver. In 1915 Kingsbury and Bell [34] found hippuric acid in relatively large amounts in the liver after injections of aminoacetic acid and sodium benzoate; they suggested in their turn that the kidney was not the only organ in which the synthesis might occur. In 1918 Lackner, Levinson and Morse [35] poisoned dogs with hydrazine sulfate, which is known to affect only the liver and to leave the kidney intact, and found the synthesis of hippuric acid greatly diminished after the hepatic damage had been established. They considered their findings entirely in line with what is known of the characteristic synthetic function of the liver as compared with that of the kidney. In 1921 Delprat and Whipple,[36] experimenting with necrosis of the liver, caused by chloroform, also found that under these circumstances the synthesis of hippuric acid was much delayed.

In 1925 Bryan,[37] who was using the hippuric acid test as it had been used prior to that time, to determine renal function, found in 6 of 10 cases in which hepatic involvement was known to exist a constant and definite decrease in the excretion of the acid. At this time he advanced the hypothesis that the decrease might possibly be due to hepatic dysfunction, but until Quick's work was published there was still no suggestion that the method might be used for such a determination.

In 1932, in a study of the conjugation of benzoic acid in man, Quick found that the excretion of hippuric acid proceded at a constant rate irrespective of the amount of sodium benzoate administered. He found, further, that the output of hippuric acid was greatly increased by the ingestion of aminoacetic acid or of foods rich in it. The conclusion seemed inevitable that the rate of formation of hippuric acid is dependent on the speed with which the organism can synthesize aminoacetic acid. Since it is established that the main site of the synthesis of aminoacetic acid is the liver, Quick reasoned that various degrees of hepatic damage would be likely to show a corresponding diminution in the excretion of hippuric acid and that the hippuric acid test, hitherto employed as a test of renal function, actually should be a more delicate test of hepatic function.

The logic of the reasoning is clear. The synthesis of hippuric acid is a process of detoxification which is brought about by the conjugation

34. Kingsbury, F. B., and Bell, E. T.: Synthesis of Hippuric Acid in Nephrectomized Dogs, J. Biol. Chem. **21**:297, 1915.

35. Lackner, E.; Levinson, A., and Morse, W.: Role of Liver in Hippuric Acid Synthesis, Biochem. J. **12**:184, 1918.

36. Delprat, G. D., and Whipple, G. H.: Studies of Liver Function: Benzoate Synthesis and Hippuric Acid Synthesis, J. Biol. Chem. **49**:229, 1921.

37. Bryan, A. W.: Clinical and Experimental Studies on Sodium Benzoate: Value of Sodium Benzoate Test of Renal Function, and Effect of Injury of Liver on Hippuric Acid Synthesis, J. Clin. Investigation **2**:1, 1925.

of benzoic acid and aminoacetic acid. The product of the conjugation is eliminated in the urine as hippuric acid except for a small fraction which is conjugated with glycuronic acid and eliminated as glycuronic acid monobenzoate. There is no store of preformed aminoacetic acid in the body; the liver has a maximum hourly synthesis of endogenous aminoacetic acid and in the absence of an exogenous supply cannot produce more than this maximum amount to combine with the ingested benzoic acid. The rate of synthesis of hippuric acid is therefore governed by the ability of the organism to produce aminoacetic acid. Since the liver is the site of the synthesis of this acid, it can reasonably be assumed that the synthesis will be adversely affected in the presence of certain types of hepatic damage and that the output of hippuric acid, which will be correspondingly diminished because of the lack of aminoacetic acid to combine with benzoic acid, will serve as an index of this damage.

The equations may be expressed as follows:

1. Sodium benzoate → benzoic acid + aminoacetic acid → hippuric acid.

2. Sodium benzoate → benzoic acid + glycuronic acid → glycuronic acid monobenzoate.

The author of the test, anticipating the objections likely to be raised to it, himself competently replied to them. The first possible objection is that the reserve of the liver is so great that impairment can be demonstrated only after extensive damage. This is true, Quick granted, in the sense that large portions can be removed surgically without lethal consequences, but proof exists that certain mechanisms are so delicate that there is practically no margin of safety. He adduced the experiments of Smyth and Whipple, which showed that a dose of chloroform too small to produce changes in the hepatic epithelium can cause a marked reduction in the excretion of the bile acids, and his own similar experiments, which produced a marked reduction in the output of glycuronic acid even when there were no histologic changes in the liver. The test indicates, he pointed out further, that the mechanism of the synthesis of aminoacetic acid seems to have no great margin of reserve, since the marked reduction in the excretion of hippuric acid in cases of catarrhal jaundice is out of all proportion to the characteristic structural changes in this type of pathologic condition.

The second possible objection is that the test indicates only one function of the liver. This is certainly true, Quick replied, but the hepatic functions are so intimately related to each other that injury to one mechanism may conceivably affect others. Thus the synthesis of amino acids, such as aminoacetic acid, depends on a precursor presumably derived from the metabolism of carbohydrates, while the forma-

tion of bile acids requires an ample supply of aminoacetic acid and taurine. The mechanism which synthesizes glycocholic acid is probably the same as that which effects the conjugation of benzoic acid and aminoacetic acid. Quick stated that it is significant that long-continued obstructive jaundice, which, as shown by Greene, Walters, Ravdin and others, brings about a decrease in the formation of bile acids, also brings about a reduction in the output of hippuric acid, neither substance returning to a normal level until a considerable time after the relief of the obstruction.

It is clear that the test is based on a normal physiologic process and for that reason involves no strain on the liver, such as is involved in almost all the other accurate tests for hepatic function, which require what we may describe as a superperformance. On the other hand. it would be foolish not to admit such valid objections as Mann's, that no conclusive proof yet exists that the liver is the sole site of the synthesis of hippuric acid. It would also be desirable, Mann added, to study the test in relation to the physiologic state of the liver at the time of its performance, as well as to have more information in regard to the rate of elimination of hippuric acid in the toxic nephroses, which are frequently associated with hepatic injury.

PRACTICAL CONSIDERATIONS IN THE USE OF THE QUICK TEST

The mention of renal disease brings to mind the precaution that the test should always be checked from that standpoint. Quick suggested a coincident determination of the nonprotein nitrogen content of the blood. We ourselves prefer, as did Kohlstaedt [38] and Helmer, the urea clearance test of Van Slyke.[39] We believe it more delicate, in view of Van Slyke's demonstration that as much as 20 per cent of renal damage can occur without alteration of the nonprotein nitrogen content of the blood. If renal damage is also present, the hippuric acid is retained as a nitrogenous product would be, and the test must be interpreted in the light of that fact. Snell, discussing the same subject, mentioned the work of Snapper and Grünbaum, who contended that there is some relation between the elimination of water and the elimination of hippuric acid. He suggested that erroneously low values may be obtained for patients who are dehydrated and who secrete only small amounts of urine, but this objection does not seem to us valid if the kidneys retain their power of concentration.

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38. Kohlstaedt, K. G.: A Study of the Hippuric Acid Excretion as a Test of Hepatic Function, Am. J. Digest. Dis. & Nutrition **3**:501, 1936.

39. Van Slyke, D. D., and others: Studies of Urea Excretion: Comparison of Blood Urea Clearance with Certain Other Measures of Renal Function, J. Clin. Investigation **8**:357, 1930.

We have used the precipitation technic described by Quick and not the extraction method, which Kohlstaedt and Helmer considered more accurate in cases of jaundice; that has not been our experience. It is necessary, of course, that the specimens be stirred vigorously to precipitate the full amount of hippuric acid crystals; failure to observe this precaution is undoubtedly responsible for some inaccurate and misleading results. We also concentrate all specimens in which the crystallization is grossly small.

We formerly followed the exact technic described by Quick and collected and studied hourly specimens; for the last six months, after a series of careful comparative tests, we have been using a single four hour determination. We have found this method equally accurate and far simpler. It reduces the work in the laboratory and in the wards, which is a real consideration when nursing facilities are as limited as they frequently are in public hospitals. It also removes the objection, which is rather serious and frequent, that catheterization may be necessary to secure the hourly specimens at the appointed times; the risk thus introduced, especially when repeated tests are made, needs no comment. We have also found that the specimen can be stored in the ice box for hours or even for several days without affecting the accuracy of the test.

Sodium benzoate is nontoxic, and smaller doses are required for the test, Quick pointed out, than are administered therapeutically. It is inexpensive, which gives it an enormous advantage over the admittedly accurate bilirubin test. Hirscheimer has shown in his study of the use of this test for pregnant subjects that the drug can be administered intravenously, but we have not so employed it. He lists as possible sequelae diarrhea, anorexia and vomiting, as the result of local irritation of the gastrointestinal tract, and such symptoms referable to the central nervous system as headache, tinnitus, vertigo and reflex vomiting. Even with the repetition of the test, which is our custom, we have not seen such serious symptoms in any case.

In fact, the only case in our long series in which there was even a suggestion that the test had been dangerous is not particularly convincing. A Negro aged 66, with jaundice of undetermined duration, was operated on after a diagnosis of carcinoma of the pancreas had been made. Although he was an admittedly poor surgical risk, he had no special preparation except one infusion of dextrose. His preoperative hepatic function was 0.636. At operation the pancreas was demonstrably normal, and the symptoms were discovered to be due to a marked hepatic cirrhosis, for which cholecystostomy was done. The Quick test on the first day after operation was 0.435; one infusion of dextrose had been given. On the fourth day it was 0.437, and on the day before death, 0.257. Only one other infusion of dextrose had

been given during this period. One hour after each of the last two test doses had been administered the patient began to vomit, but there seems no doubt that by that time practically all of the sodium benzonate had passed out of the stomach. That the drug had a bad effect on the gastrointestinal tract of a seriously ill patient we are entirely willing to grant. That it had any part at all in the fatal outcome, as was suggested, seems unworthy of serious consideration; our own theory in this case, the only one in which such a question has arisen, is that a more liberal postoperative use of dextrose might have kept the patient alive for a longer period.

It must be granted, however, that we have been handicapped, at intervals, by the loss of the dose by vomiting, though for the most part this accident has occurred only in certain wards and then in epidemic waves strongly suggestive of a psychic or hysterical origin. The dose is usually retained if nurses and fellow patients refrain from helpful suggestions as to its nauseous effects. At one time we were obliged to discontinue the test for a period of weeks in a ward for white women because of the state of near-hysteria over it to which an excitable intern had reduced the patients, not one of whom was seriously ill and all of whom were being used for controls. In the wards for men and for Negresses it is unusual to have any trouble.

We have somewhat overcome the unpleasant taste of the sodium benzoate by the addition of a small amount of cherry syrup. Capsules are not practical. The required amount of the drug could not be put into fewer than six very large capsules, and the amount of water required to wash them down would probably alter the results of the test. We have wondered, in this connection, whether the slight dilatation of the stomach usually present after operation, as well as the alteration in absorption due to the physiologic alteration of the stomach under these circumstances, might influence the results, but the four hour period occupied by the test would seem to eliminate that possibility. We have had little trouble in giving the test even on the first day after operation, but we often withhold it because of the unwisdom of putting even small quantities of fluid into the stomach or because of the impossibility of forbidding the use of fluids for seriously ill patients for such a length of time.

We cannot say too emphatically that a single test does not furnish adequate information as to the state of the liver. Our own custom is to make the test on admission, after preparation for operation, and on the first, second, third, seventh and fourteenth days after operation, according to the length of the patient's stay in the hospital. We are willing to accept a single high or normal reading as correct if we are certain that there has been no unusual ingestion of carbohydrates, orally or otherwise, but we are unwilling to accept a single low reading as

correct, and we promptly repeat the test when such a result is noted. We check any possible loss of the sodium benzoate by vomiting or by failure to drink all of the solution; for several months we have made it our custom to have the receptacle in which the dose was given returned to us unwashed and still marked with the patient's name, so that we can check this point for ourselves. Also, to avoid possible errors in solubility, we use the patient's own urine to rinse out the beaker in which the precipitation is done, to be sure that the entire amount goes through the filter.

REPORTED RESULTS WITH THE QUICK TEST

Quick's first clinical report on this test included 36 cases, and his second,[40] 100 cases, some 80 of which were cases of hepatic or biliary disease. In the light of increasing experience he has seen no reason to alter his original opinion of the value of the test as an index of hepatic function and as a guide to diagnosis and prognosis. We agree with him that a low reading, particularly when it improves under correct preoperative preparation, does not necessarily indicate a fatal outcome, though we do regard it as a storm warning.

Vaccaro[41] employed the Quick test in a group of 44 cases, in 27 of which the gallbladder and bile passages were involved. Twenty-six patients in the latter group of cases came to operation or autopsy, and there was a rather surprising accord between the results of the test and the operative and autopsy observations.

Snell and Plunkett[42] used the test in a series of 38 cases of various types of jaundice. They said that it is a reasonably accurate and satisfactory index of parenchymatous hepatic damage, especially in the surgical types of jaundice. They noted little correlation between the results of this test and those of the galactose tolerance test but general agreement between the results and those of the serum bilirubin test. Our own idea is that if the Quick test and the bilirubin test could be used in combination for all patients they would furnish every reasonable safeguard from the hepatic standpoint, but the cost of the bilirubin test makes this plan impractical.

Kohlstaedt and Helmer used the Quick test in 77 cases, 41 of which were instances of disease of the liver and biliary tract. They reported a stormy postoperative course, and also some fatalities of the "liver death"

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40. Quick, A. J.: Clinical Value of the Test for Hippuric Acid in Cases of Disease of the Liver, Arch. Int. Med. **57**:544 (March) 1936.

41. Vaccaro, P. E.: The Synthesis of Hippuric Acid, Surg., Gynec. & Obst. **61**:36, 1935.

42. Snell, A. M., and Plunkett, J. E.: The Hippuric Acid Test for Hepatic Function: Its Relation to Other Tests in General Use, Am. J. Digest. Dis. & Nutrition **2**:716, 1935.

variety, in patients with low readings. They stated that the test is reliable and of value for the detection of latent hepatic damage before clinical signs are evident.

Yardumian and Rosenthal [43] used the Quick test in 68 cases, 18 of which were instances of disease of the liver and biliary tract. They found the test reliable both independently and in comparison with other tests and reported it to be valuable in the differential diagnosis of hepatic and obstructive jaundice.

PERSONAL STUDIES WITH THE QUICK TEST

To date we have used this test in 82 cases of disease of the liver and biliary tract, of which the cases in which operation was performed are presented graphically (chart 1). Reducing the findings thus depicted

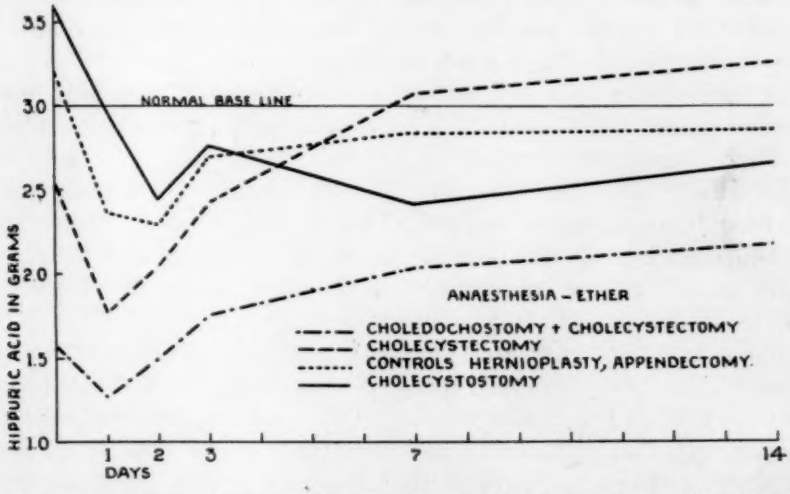

Chart 1.—Preoperative and postoperative results of the Quick hippuric acid test for hepatic function in cases in which operation was performed on the biliary tract.

to percentages of normal liver function gives the figures shown in table 1.

A study of these figures leads to some interesting and surprising conclusions. Highly significant in all cases, including those of the ether controls, which we shall discuss in detail in a later paper, is the marked impairment in hepatic function after operation. The drop on the first day is less marked after cholecystostomy than after other procedures, for obvious reasons. This operation is done on patients who are either very well prepared or respond very well to preparation. It involves less

43. Yardumian, K., and Rosenthal, P. J.: Hippuric Acid Elimination as a Test for Liver Function, J. Lab. & Clin. Med. **22**:1046, 1937.

manipulation, time and trauma than do other biliary procedures. But the slow return to normal, even four weeks after operation, suggests the doubtful wisdom of prolonged drainage of the biliary tract and supports Judd's contention that there is rarely an occasion for cholecystostomy except as a temporary operation.

We are unprepared to make definite statements concerning the reason for the postoperative impairment of liver function. We doubt that any significant amount of hippuric acid is lost in the excreted bile. Perhaps infection is the cause. Perhaps the tube, which is a foreign body, sets up a reaction which spreads upward into the ducts. Probably the alteration of pressure in the biliary tree causes a loss of bile in the gastrointestinal tract, with a resulting decreased assimilation of fat. Since the metabolism of fat is related to the storage of carbohydrates, the glycogen in the liver is automatically diminished and the hepatic function correspondingly impaired. Whatever the reason, it might be well

TABLE 1.—*Percentages of Normal Hepatic Function*

Procedure	Preoperative		Postoperative (by Days)					
	1	2†	1	2	3	7	14	28
Cholecystectomy	77.5	....	51.7	60.0	71.2	90.2	96.0	....
Drainage of the common duct	40.0	46.0	36.6	51.4	....	60.0	64.0	71.0
Cholecystostomy	77.2	107.7	87.0	72.0	82.0	71.0	78.0	81.0
Ether controls*	95.0	....	70.0	67.4	79.3	83.4	83.4	....

* Practically all biliary operations in this service are done with the patients under ether anesthesia.
† After preparation.

to bear in mind the effect of cholecystostomy on the liver, as shown by these tests, and to reflect that it may not be the simple and safe procedure it is usually assumed to be.

These figures show the importance of preoperative preparation and postoperative care in cases of biliary disease. The patients treated by means of cholecystostomy or operations on the common duct were all carefully prepared for operation, because, presumably, their state was more serious than that of patients on whom cholecystectomy was performed, most of whom appeared to be good risks. After all biliary operations it is our custom to give dextrose intensively for the first day or two, and thereafter according to the indications. Except for the preliminary preparation and the postoperative bolstering of the liver by this therapy, the postoperative drop in function might have been far more marked and might have had far more serious consequences. As it is, the drop to 36.6 per cent of normal in the cases of operation on the common duct suggests the enormous reserve power of the liver, on which we have repeatedly commented, and its ability to carry on under the most adverse circumstances. Just how far that reserve

extends is a matter on which we are not at this time prepared even to speculate. The fall in hepatic function after cholecystostomy on the second day after the operation, when intensive dextrose therapy is usually discontinued except on special indications, is also striking. Our figures support the hypothesis that the degree of hepatic damage in terms of functional impairment is proportionate to the duration of the biliary disease (chart 2). When the obstruction had lasted for an average of two and two-tenths years the hepatic function averaged 2.626, 76.5 per cent of normal; when it had lasted for four and a half years the hepatic function averaged only 2.170, 63 per cent of normal.

The cases of toxic and catarrhal jaundice and those of miscellaneous hepatic conditions need no special comment (table 2). Unlike other observers, we found the values in cases of obstructive jaundice slightly

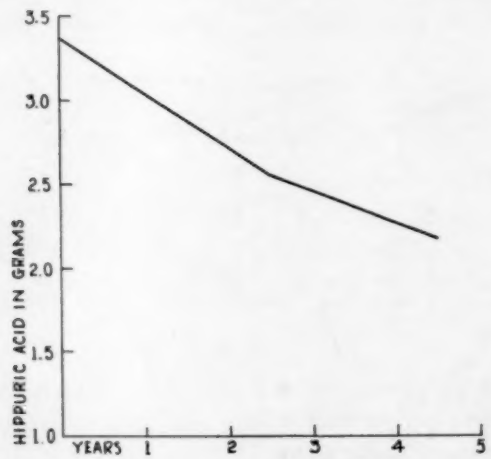

Chart 2.—Relation between the state of hepatic function and the duration of disease of the biliary tract, as shown by the Quick hippuric acid test.

lower than in cases of the toxic and catarrhal varieties, perhaps because of a possible longer duration in our cases. It is rather surprising, however, to find such low values with conditions of such relatively brief duration as are the toxic and catarrhal varieties of jaundice. We do not share Quick's opinion that the test is helpful in distinguishing between obstructive jaundice, in the presence of which the hippuric acid values are likely to be high, and toxic jaundice, in the presence of which they are markedly reduced, and should be unwilling to determine our therapeutic course on this basis. Snell and Plunkett shared our views.

We are inclined to lay no special stress on the relation between the icteric index and the values for the hippuric acid test of function. In cases of toxic hepatitis, in which the icteric index averaged 78, the hepatic function averaged 1.717, 50 per cent of normal. In cases of

TABLE 2.—*Typical Cases of Various Types of Jaundice and of Hepatic and Biliary Disease*

No.	Race	Sex	Age	Duration of Illness	Diagnosis	Quick Test	Comment
1	White	Male	61	4 months	Toxic hepatitis	0.692	Autopsy confirmation; icterus index 111
2	White	Female	18	?	Toxic hepatitis	1.462	Wassermann test ++++; icterus index 83
3	White	Male	26	10 days	Toxic hepatitis	2.898	Prompt recovery
4	White	Female	23	5 weeks	Toxic hepatitis	2.937	Following treatment for malaria; test after recovery
5	White	Female	64	2 years	Toxic hepatitis	1.956	Acute attack 20 days previously; previous cholecystectomy; icterus index 67
6	White	Female	49	3 months	Toxic hepatitis	1.761	Icterus index 33
7	White	Female	21	1 week	Toxic hepatitis	1.307	Wassermann test ++++; icterus index 250
8	White	Male	56	1 week ?	Catarrhal jaundice	0.726	Icterus index 250
9	White	Female	27	1 week	Catarrhal jaundice	0.758 0.905	Icterus index 200
10	White	Male	27	2 weeks	Catarrhal jaundice	3.382	Icterus index 166; test after intensive dextrose therapy
11	White	Female	16	2 weeks	Catarrhal jaundice	0.806	Wassermann test ++++; icterus index 90.9; puerperal infection 6 months previously
12	Negro	Male	24	2 weeks	Obstructive jaundice	2.459	Wassermann test ++++; icterus index 100; test after clinical recovery
13	Negro	Male	33	3 weeks	Obstructive jaundice	2.488	Icterus index 250
14	White	Female	60	25 years	Obstructive jaundice	1.526	Icterus index 56; common duct stone
15	White	Female	42	2 months	Obstructive jaundice	2.266	Acute cholecystitis; icterus index 23
16	White	Male	43	3 years	Hepatic cirrhosis	2.168	
17	White	Male	49	?	Hepatic cirrhosis	2.154	Admitted for scalp lesion; cirrhosis discovered in course of examination
18	White	Male	49	5 months	Biliary cirrhosis	1.061	Ascites; chronic alcoholism
19	White	Male	64	6 months	Biliary cirrhosis	0.715	Ascites; chronic alcoholism; repeated paracentesis; left hospital against advice, critically ill
20	Negro	Male	66	5 days	Biliary cirrhosis	0.636 0.435 0.437 0.259	Preoperative; one infusion 2d, 4th and 5th days after cholecystostomy, under ether; two infusions during this period; death 24 hours later
21	White	Female	31	6 months	Pyogenic abscess of liver	2.111 1.806	After repeated drainage
22	Negro	Male	29	10 weeks	Amebic abscess of liver	1.517	Died after 2d drainage

obstructive jaundice, in which the icteric index averaged 141, the hepatic function averaged 1.489, 43.2 per cent of normal. In cases of catarrhal jaundice, in which the icteric index averaged 140, approximately the same as in the obstructive type, the hepatic function averaged 1.697, 49.2 per cent of normal, practically the same as in the toxic type.

One or two illustrative cases may be mentioned. The most striking instance of failing hepatic function was furnished by a Negress aged 27, who had had epigastric distress for four months and jaundice for three weeks, associated with a considerable though undetermined loss of weight. She had a very large and tender liver. The icteric index was 67 on admission, and rose successively to 80 and then to 100. The urea content of the blood was 14.7 and the red blood cells 3,610,000. The Quick test reading was 0.5; we were just beginning to employ the test, and we did not appreciate the significance of this finding until later, when the patient died a typical "liver-kidney death" after cholecystostomy, which was done on a diagnosis of hepatic cirrhosis. The bile drainage became increasingly light and scanty, the urea content of the blood rose to 38, and for the last three days of life the patient was practically anuric, in spite of fluids given intensively by vein. Autopsy was not permitted, but the clinical syndrome was unmistakable. We tested this patient by the serum volume test for the hemorrhagic diathesis in jaundice, which we have just reported,[44] and, as we had predicted, there was no tendency to hemorrhage.

A white man aged 59, with a history of heartburn and painless jaundice for two weeks and no other symptoms of any sort, was also tested by the serum volume test. He showed an initial tendency to hemorrhage but none after preparation, and there was no bleeding at operation or afterward. The first Quick test gave a reading of 0.786, which by intensive preparation was raised to 1.859. This patient had had a cholecystostomy twenty years before, and at operation the anatomic distortion was so great that complete exploration of the common duct was impossible. Cholecystenterostomy was therefore done. He died in fifty-six hours, with typical hyperpyrexia; the temperature rose to 106 F. by axilla. Postmortem examination revealed no evidence of infection or hemorrhage, and the only positive finding was the hepatic necrosis which we have come to regard as typical of the so-called "liver death." Whether the hepatic damage as revealed by the first Quick test was too extensive to be overcome even by careful preparation we cannot say; the improvement in function as revealed by the second test may have been more apparent than real. Perhaps the patient's failure to respond to dextrose therapy as well as to decholin sodium (sodium dehydrocholate), with which we have had excellent results in

44. Boyce, F. F., and McFetridge, E. M.: A Serum Volume Test for the Hemorrhagic Diathesis in Jaundice, J. Lab. & Clin. Med. **23**:202, 1937.

some similar cases, was due to an inability of the liver to take care of the carbohydrates supplied. Kramer and his associates [45] have reported 2 such cases, in which the patients were children, and repeated blood sugar determinations might have settled this point.

Against these unfortunate cases may be set another. A 46 year old white woman told a rather indefinite story suggestive of a pathologic condition of the biliary tract of several years' duration. The icteric index was 200 at operation, and we regarded her as a frankly poor surgical risk, although the initial hepatic function of 0.671 had been raised by preparation to 1.708 and the serum volume test had revealed no tendency toward hemorrhage. Operation revealed an obstruction of the common hepatic duct, the type of which was not exactly determined; the duct was successfully drained after tedious dissection. Intensive dextrose therapy was continued for ten days after operation, and the convalescence was gratifying from every standpoint. The first postoperative Quick test, on the third day, showed a drop in the hepatic function to 1.219. Thereafter there was a small but steady rise, and when the patient was discharged, five weeks later, the reading was 2.283, more than three times as high as the initial reading. She has remained well to date, now eight months later. Why this patient, with a liver function on admission and after preparation slightly lower than those of the second patient described, should have gone on to uneventful recovery while the other patient lost his life is a problem for which we have no solution.

DEXTROSE THERAPY IN HEPATIC DYSFUNCTION

Our studies with the Quick test have made it clear that the premises on which dextrose has been used to bolster the liver are entirely sound. The clinical results of this mode of therapy are well known; the effect on the hepatic function of its use and withdrawal are shown by our figures, and research workers have had dramatic illustrations of what it can achieve. In recent (unpublished) work of our own on temperature reactions in hepatectomized dogs, we were able by this method to revive animals apparently at the point of dissolution eight and ten hours after operation. Their condition improved while the injection of dextrose was being made, and when it was finished they got to their feet and walked about the cage.

Althausen's [46] studies on dextrose therapy are very valuable. In one set of experiments he showed that insulin not only does not increase

45. Kramer, B.; Grayzel, H. G., and Solomon, C. I.: Chronic Hypoglycemia in Childhood, J. Pediat. **5**:299, 1934.

46. Althausen, T. L.: Effects of the Administration of Glucose and Glycogen Content of Normal and Experimental Damaged Livers, Ann. Int. Med. **6**:193, 1932; Dextrose Therapy in Diseases of the Liver, J. A. M. A. **100**:1163 (April 15) 1933.

the hepatic glycogen but has precisely the opposite effect; his results suggest that the supposed beneficial effect of dextrose-insulin therapy is achieved by the dextrose in spite of the insulin. In another series of studies he was able to show the comparative effects of dextrose given by mouth and by vein. Biopsies of material taken at operation showed that patients who had received it intravenously for various periods had livers which showed moderate amounts of glycogen, while patients who had received it chiefly by mouth exhibited liver cells literally stuffed with glycogen. He suggested as a corollary to these findings that surgeons might remember the simpler method of oral administration before they resort to the more troublesome method of intravenous administration.

Jones [47] supplied further proof of the value of dextrose in cases of hepatic disease. In an analysis of 83 cases of hepatic insufficiency he found a 95 per cent mortality in the cases observed between 1922 and 1929, when dextrose was used in small quantities if at all, against a mortality of 63 per cent in the similar cases studied since that date, when dextrose therapy has been given as a matter of routine. In 1 case in our own series the patient has received so much benefit from the simple oral administration of carbohydrates that he has flatly declined the operation advised; his clinical improvement has been paralleled by the improvement in his hepatic function.

RELATION BETWEEN HEPATIC AND RENAL DYSFUNCTION

Jones brought up another matter which is mentioned by very few writers but which we ourselves think very important, the relation between hepatic function and urinary output. He went so far as to say that the prognosis in cases of hepatic disease can be based on the occurrence or failure of spontaneous diuresis, and he cited cases and statistics to prove his point. We have noted the same relationship in a large number of cases, some of them included in this series. Similar cases have been reported to us by other physicians who know of our interest in this matter.

An illustrative case might be mentioned. A white man aged 63, with a history of disease of the gallbladder for four years, had jaundice for the first time just before admission; there was no evidence of it clinically or otherwise after hospitalization. For many reasons he was regarded as a poor surgical risk, although routine tests, including the urea clearance test, gave normal values. The initial value for hepatic function was 0.847; after intensive preparation for ten days it was raised to 2.212. We might say at this point that we have no clear idea why

47. Jones, C. M.: Newer Concepts of Liver Disease, New England J. Med. **215**:432, 1936. Jones, C. M., and Eaton, F. B.: Prognostic Significance of Spontaneous Diuresis in Acute or Subacute Disease of Liver, ibid. **213**:907, 1935.

some patients respond to preparation so well and others so poorly. Cholecystectomy, choledochostomy and drainage were done. The gall-bladder and ducts were full of sand and a friable, necrotic material strongly suggestive of malignant tumor, although this diagnosis was later disproved in the laboratory.

The patient's immediate postoperative reaction was not good. He was listless and oliguric; the drainage of bile was scanty, and the prognosis was doubtful. The reading for the Quick test on the second day was 0.782. At this time we saw the patient in consultation and suggested the use of decholin sodium. Within four hours there was a free flow of bile, the patient had a large, spontaneous diuresis, and the entire clinical picture had changed; in particular, the distressing listlessness had entirely disappeared. The convalescence was stormy, being complicated by an infection of the upper respiratory tract and a partial wound rupture, but the tendency to recovery was clear. Injections of decholin sodium were given every eight hours for twenty-four hours. The value for hepatic function on the third day after the operation had risen to 1.749, and although it fluctuated and at no time rose above 2.289, it never again fell to a disturbingly low level. The patient has remained well from the standpoint of his biliary disease, although three months after his discharge he exhibited a malignant tumor of the larynx, from which at the time of writing he is slowly dying.

Many explanations have been advanced of the relation between hepatic and renal function. We are particularly impressed with that of Bruhl and of Watzadse, which Vaccaro quoted. They found in their experimental work on frogs that a lack of aminoacetic acid brought about a cessation of glomerular circulation. On this basis it seems not unreasonable to assume that the liver, by means of the amount of aminoacetic acid released into the circulating blood stream, actually determines renal function. If this is true, we are justified in interpreting the progressive oliguria, passing over into anuria, which is the outstanding characteristic of the "deferred liver death" or "liver-kidney" syndrome, as due to a diminished synthesis of aminoacetic acid in the liver.

We have heretofore explained this syndrome on the basis of the inability of the liver to take care of the products brought to it for detoxification and the resulting damage of the convoluted tubules of the kidney caused by the undetoxified products shunted on to the kidney by the failing liver. We did not accept the theory of Helwig and his co-workers, that these toxins have a special affinity for the kidney. We were never fully satisfied with our explanation, however, for we did not consider that the renal damage, as manifested by histologic study, was sufficient alone to account for the marked depression of renal function that is clinically apparent. It now seems to us more reasonable to assume that the impairment of the synthesis of aminoacetic

acid by the liver, as manifested by a decreased excretion of hippuric acid, is the basic deficiency. Certainly the improvement following the administration of decholin sodium, with, as has been proved, the resulting improvement first in the synthesis of aminoacetic acid and then in the formation of bile acids, would seem to support this view, entirely aside from the actual clinical results we have repeatedly witnessed after the use of this agent.

Whatever be the truth of this hypothesis, the important consideration is that a patient who exhibits a damaged hepatic function before operation, as manifested by a failure of synthesis of aminoacetic acid, becomes a doubly poor risk if there are also apparent signs of renal damage, such as a raised urea content in the blood and a low urea clearance.

SUMMARY

The increasingly important role of the liver in biliary surgery is pointed out.

The functions of the liver are outlined, and its capacities and reserve power are discussed.

The value and limitations of tests for hepatic function are considered.

The advantages and disadvantages of the tests in general use are outlined.

The development of the Quick hippuric acid test of liver function is sketched; its advantages and disadvantages are listed, and special phases of our experience with it are discussed.

The results of our personal experience with the test in cases of biliary and hepatic disease are set forth, and such special points are discussed as preoperative preparation, the postoperative drop in function, the relation of functional impairment to duration of illness and the extreme importance of dextrose therapy preoperatively and postoperatively. Illustrative cases are reported.

The close relation between hepatic and renal function is pointed out, and experimental and clinical proof of this relation is outlined. The generally good results following the use of decholin sodium are noted, and it is suggested that patients suffering from both hepatic and renal dysfunction should be regarded as dubious risks for operation.

NOTE.—Shortly after this paper was written, Dr. Quick supplied us with an intravenous test, a modification of his original test. This modification permits the use of the test immediately after operation and for seriously ill patients and therefore meets certain of the objections we have outlined. We have used the intravenous Quick test in approximately 50 cases of disease of the thyroid gland and biliary tract and have found it as satisfactory as the oral test.

STUDIES OF HEPATIC FUNCTION BY THE QUICK HIPPURIC ACID TEST

II. THYROID DISEASE

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AND

ELIZABETH M. McFETRIDGE, M.A.

NEW ORLEANS

In a previous communication [1] we have discussed in detail the rationale of the Quick hippuric acid test for hepatic function and have considered its reliability as an index of hepatic damage in cases of hepatic disease and of disease of the biliary tract. In this second communication we shall consider its value as an index of hepatic function in the presence of thyroid disease, for which purpose we have been employing it for the past eighteen months. Before discussing it from this aspect, however, it is necessary to consider the justification for any test of hepatic function under these circumstances, which means that we must trace the relation between the liver and the thyroid gland.

It is surprising to find how commonly that relation is ignored. The majority of writers list hyperthyroidism as the chief cause of death of toxic thyroid disease, but they make no attempt to explain the origin of the state called thyroid crisis. On the other hand, Dinsmore,[2] in the chairman's address before the Section on Surgery of the American Medical Association in 1937, made the unqualified statement that the most common cause of postoperative delirium and disorientation after operations on the thyroid gland is hepatic failure, and Lahey [3] has repeatedly stated his belief that deaths associated with hyperthyroidism are chiefly "liver deaths." These physicians are authorities in the field of thyroid disease, and they know whereof they speak. We share their

From the Department of Surgery of the School of Medicine, Louisiana State University, and the Charity Hospital of Louisiana.

1. Boyce, F. F., and McFetridge, E. M.: Studies of Hepatic Function by the Quick Hippuric Acid Test: I. Biliary and Hepatic Disease, Arch. Surg., this issue, p. 401. This contains an extensive list of references which are not repeated here.

2. Dinsmore, R. S.: Factors Influencing Morbidity in Thyroid Surgery, J. A. M. A. **109**:179-183 (July 17) 1937.

3. Lahey, F. H.: Reduction of Mortality in Hyperthyroidism, New England J. Med. **213**:475-479 (Sept.) 1935.

opinion. The sudden and extreme hyperpyrexia which may occur postoperatively and even preoperatively, the jaundice, which is sometimes slight and transient but more often deep and terminal, and the benefit produced in cases of thyroid disease by the measures ordinarily used to combat hepatic damage, all seem to establish the thesis.

We became interested in this aspect of thyroid disease in the course of our studies on the "hyperpyrexic death," or "liver death" which sometimes follows operation on the biliary tract. The same type of clinical picture, dominated by hyperpyrexia with a rapidly fatal outcome, has become classic in the literature on thyroid disease, under the terms postoperative crisis or thyroid storm, and the same type of microscopic hepatic damage noted after such deaths in cases of biliary disease can be noted after similar deaths from thyroid disease. The same clinical and pathologic picture is also seen in cases of untreated or mismanaged thyroid disease for which operation has not been done.

HISTORICAL DATA CONCERNING THE HEPATOTHYROID RELATION

The whole subject of hepatic changes in cases of toxic thyroid disease has recently been reviewed by Cameron and Karunaratne.[4] As they pointed out, Paul in 1865 was the first to mention the association of hepatic cirrhosis and toxic thyroid disease. Three years later Trousseau again referred to the possible association. Jaundice was first mentioned by Habershon[5] in 1874, and Burton[6] in 1888 reported its transient occurrence in a male patient with exophthalmic goiter. White[7] in 1886 had described the same disease as occurring in a woman aged 47, in whom autopsy revealed hepatic cirrhosis. In 1898 Sutcliff[8] reported "an extraordinarily acute case of Graves' disease" in a female patient who exhibited exophthalmos, emaciation, a racing pulse, persistent vomiting and antemortem jaundice, the whole illness occupying only three months. Eder[9] in 1906, in a report of 3 cases of jaundice in which the condition was associated with exophthalmic goiter, seems first to have realized the causal relationship, though his idea of the basis

4. Cameron, G. R., and Karunaratne, W. A. E.: Liver Changes in Exophthalmic Goitre, J. Path. & Bact. **41**:267-282 (Sept.) 1935.

5. Habershon, W.: Exophthalmic Goiter; Heart Disease; Jaundice; Death, Lancet **1**:510, 1874.

6. Burton, F. W.: Pigmentation and Other Cutaneous Affections in Graves' Disease, Lancet **2**:573, 1888.

7. White, W. H.: On the Prognosis of Secondary Symptoms and Conditions of Exophthalmic Goiter, Brit. M. J. **2**:151-153, 1886.

8. Sutcliff, E. H.: An Extraordinarily Acute Case of Graves' Disease, Lancet **1**:717, 1898.

9. Eder, M. D.: Three Cases of Jaundice Occurring in Persons Suffering from Exophthalmic Goiter, Lancet **1**:1758, 1906.

thereof, some toxemia of the intestinal canal "with the seat of action in the pituitary body," would need considerable editing today. This author noted that although jaundice was not mentioned in English texts as a possible accompaniment of toxic goiter, it had been referred to by Dieulafoy in his "Pathologie Interne" published in 1901.

Marine and Lenhart [10] in 1911, in a study of the pathologic anatomic picture in the presence of exophthalmic goiter, noted a well marked generalized thickening of Glisson's capsule in 5 cases, in 4 of which atrophic cirrhosis was present. Such livers, they pointed out, tended to be reduced in volume, and the cells usually exhibited some degree of fatty metamorphosis. In 1919 Kohn [11] reported 56 cases of exophthalmic thyroid disease, in 5 of which jaundice was present, and a group of 43 miscellaneous cases, including instances of acute thyroidism as well as of nontoxic disease, in 6 of which jaundice was present. In 1922 Kerr and Rusk [12] reported acute yellow atrophy of the liver following hyperthyroidism, with marked parenchymatous degeneration of both liver and kidneys, and in a later communication Kerr [13] reported the observation of several similar cases.

Barker [14] in 1930 described the interesting case of a white female patient admitted in coma, who died in twenty-four hours. Later a history of exophthalmic thyroid disease was secured; the condition had been treated with iodine. Postmortem examination revealed a small liver, with areas of necrosis and passive congestion, and tubular degeneration of the kidneys. He considered the hepatic condition analogous to the cardiac necrosis sometimes encountered in cases of exophthalmic goiter. Forbes [15] by illustrative cases called attention in 1934 to the possible confusion, because of the similarity of the picture, between postoperative hepatic failure and a crisis of latent or potential thyroid disease, not previously suspected, after nonthyroid surgical treatment. He suggested that in all such cases compound solution of iodine U. S. P.

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10. Marine, D., and Lenhart, C. H.: Pathological Anatomy of Exophthalmic Goiter, Arch. Int. Med. **8**:265-316 (Sept.) 1911.

11. Kohn, L. W.: Gastrointestinal Symptoms in Disturbances of Thyroid, New York M. J. **110**:1066-1068, 1919.

12. Kerr, W. J., and Rusk, G. Y.: Acute Yellow Atrophy Associated with Hyperthyroidism, M. Clin. North America **6**:445-459 (Sept.) 1922.

13. Kerr, W. J.: Necrosis of Heart and Liver in Thyrotoxicosis, with Some Notes on Possible Changes in Other Organs, Northwest Med. **29**:430-431 (Sept.) 1930.

14. Barker, L. F.: Thyro-Intoxication with Necrosis and Atrophy of the Liver, Damage to Heart Muscle and Kidneys, and Terminal Bronchopneumonia, M. Clin. North America **14**:261-263 (July) 1930.

15. Forbes, R. D.: Hyperthyroidism After Abdominal Operations, S. Clin. North America **14**:1339-1346 (Dec.) 1934.

be used as a tentative therapeutic measure. Parturier and Delerue [16] in the same year stated that 30 per cent of patients with hepatic disease present signs attributable to the thyroid; they suggested the addition of liver therapy to the thyroid treatment. It was their idea that clinically the effect of the thyroid on the liver is less marked than the effect of the liver on the thyroid; "thyroid function is unlatched only when hepatic function fails." Their arguments, it seems to us, suffer from the rather general tendency to overemphasis which we have observed in most of the communications from the French school on the subject of hepatic disease.

On the experimental side, Farrant [17] in 1913 showed that thyroid-fed cats and rabbits exhibited fatty degeneration of the liver, most marked around the center of the lobules and associated in some instances with changes suggestive of tubular nephritis. In 1917 and again in 1918 Kuriyama [18] studied the effect of thyroid feeding on white rats. Within three to five days after the feeding was begun the animals all exhibited a decreased glycogen content of the liver, though control rats in which a similar loss of weight was produced by regulation of the diet showed no such depletion. Within two or three days after thyroid feeding was discontinued the hepatic glycogen returned to normal, even though the body weight was not regained. In 1921 Hashimoto [19] and later Goodpasture [20] fed albino rats with thyroid substance in an endeavor to reproduce the myocardial changes noted clinically in hyperthyroid disease; this treatment produced not only those changes but also parenchymatous changes in the liver and in the convoluted tubules of the kidneys. Himmelberger,[21] in 1932 by injecting into mice blood serum or urine from patients with exophthalmic goiter was able to demonstrate a substance capable of disturbing the glycogenic function of the liver, although no hepatic change was noted in 40 control animals which received the same sort of injections from patients without thyroid dis-

16. Parturier, G., and Delerue, J.: Les syndrômes hépato-thyroïdiens, Rev. méd.-chir. d. mal. du foie **9**:187-218 (May-June) 1934.

17. Farrant, R.: Hyperthyroidism: Its Experimental Reproduction in Animals, Brit. M. J. **2**:1363-1367, 1913.

18. Kuriyama, S.: Influence of Thyroid Feeding upon Carbohydrate Metabolism, Am. J. Physiol. **43**:481-496 (July) 1917; Influence of Thyroid Feeding upon Carbohydrate Metabolism: I. Storage and Mobilization of Liver Glycogen in Thyroid-Fed Animals, J. Biol. Chem. **33**:192-206 (Jan.) 1918.

19. Hashimoto, H.: Heart in Experimental Hyperthyroidism with Special Reference to Its Histology, Endocrinology **5**:579-606 (Sept.) 1921.

20. Goodpasture, E. W.: Myocardial Necrosis in Hyperthyroidism, J. A. M. A. **76**:1545-1551 (June 4) 1921; Influence of Thyroid Products on the Production of Myocardial Necrosis, J. Exper. Med. **34**:407-423 (Oct.) 1921.

21. Himmelberger, L. R.: Thyroid Hormone in Blood and Urine in Graves' Disease, Endocrinology **16**:264-266 (May-June) 1932.

ease. In 1935 Habán [22] was able by thyroid feeding to produce necrotic changes in the livers of cats and rabbits, as well as a marked or complete depletion of the glycogen content; the changes were less marked in guinea pigs.

For the last three or four years the relation between the liver and the thyroid has been studied intensively in groups of cases rather than casually observed in single cases such as we have listed. Thus Weller [23] in 44 autopsies on patients with hyperthyroidism found the liver normal in only 6 cases; the hepatic involvement was moderate in 16 cases and marked in 22. In a control series exactly the reverse was noted; the liver was normal in 30 cases, moderately damaged in 13 and severely damaged in only 1. Rowe [24] in a study of 4,000 cases of various diseases found the incidence of hepatic damage, even including figures which he termed "heavily over-weighted," to be at most 10.9 per cent, whereas in 644 autopsies for hyperthyroidism he found the incidence of hepatic damage to be 22.44 per cent, more than twice as high.

Beaver and Pemberton [25] from the Mayo Clinic analyzed 107 autopsies for toxic thyroid disease, the study covering ten years and including both the iodine and the preiodine period. In 98 cases, 91.5 per cent of the total number, some hepatic involvement was noted. Acute hepatic lesions occurred in all patients who had died in crisis, as well as in 96.5 per cent of the patients whose basal metabolic rates were higher than + 60. Similar lesions were present in all patients with jaundice. The authors concluded that such lesions are an integral part of the syndrome of exophthalmic goiter and may be assumed to be due directly to thyroid intoxication, since they are usually proportionate in their degree to the intensity or the duration of the thyroid disease, or both. Ragins [26] has reported 6 such cases, and Cameron and Karunaratne have added 30 cases in which autopsy was performed at the University College Hospital Medical School, London, England. They also listed 30 cases reported by Rossle and 26 by Haban.

In studying the deaths from thyroid disease for the last ten years at the New Orleans Charity Hospital in the course of our investigations

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22. Habán, G.: Leberveränderungen bei experimentellen Hyperthyreoidismus, Beitr. z. path. Anat. u. z. allg. Path. **95**:573-589, 1935.

23. Weller, V. V.: Hepatic Pathology in Exophthalmic Goiter, Ann. Int. Med. **7**:543-560 (Nov.) 1933.

24. Rowe, A. W.: Endocrine Studies: XXXV. Association of Hepatic Dysfunction with Thyroid Failure, Endocrinology **17**:1-22 (Jan.-Feb.) 1928.

25. Beaver, D. C., and Pemberton, J. deJ.: Pathologic Anatomy of Liver in Exophthalmic Goiter, Ann. Int. Med. **7**:687-708 (Dec.) 1933.

26. Ragins, A. B.: Value of Takata and Ara Reaction as Diagnostic and Prognostic Aid in Cirrhosis of Liver, J. Lab. & Clin. Med. **20**:902-913 (June) 1935.

on thyroid disease in this nonendemic area,[27] we have observed 26 clinical cases in which death was due only to thyroid crisis; we have excluded all cases in which cardiac complications, pneumonia or any other factor played a part. We have also found 6 exactly similar cases in which autopsy revealed typical hepatic degeneration. There is every reason to believe that if the larger group of patients had also been submitted to autopsy the postmortem observations would have paralleled the clinical picture. The fact that the majority of these patients, 19 of the total group of 32, died in crisis without operation is a disturbing and impressive fact, comment on which is unnecessary.

The actual pathologic changes present in such cases at autopsy are no part of our present discussion, which concerns the fact of hepatic damage rather than the details. We may say, however, that the pathologic changes in our own cases, plus those in the cases reported in the literature, although they revealed an astonishing variety of pathologic terms apparently intended to cover the same changes, may be roughly classified as fatty infiltrative changes, degenerative changes ranging from mild changes to actual necrosis, cirrhotic changes and acute yellow atrophy. Frequently the same liver revealed various degrees of all changes in different areas, and as a rule there was a significant decrease in weight.

TESTS OF LIVER FUNCTION IN DISEASE OF THE THYROID

In view of the relation between the thyroid and the liver in the presence of toxic thyroid disease, it seems important to find some method by which the state of the patient can be estimated in terms of the hepatic factor. Clinical improvement, cardiac function, a falling basal metabolic rate—all are helpful alone or in combination, but they give no information on this point, and, as all surgeons know, they are frequently fallacious and misleading. Various attempts have been made to test hepatic function, but none with complete success. Ragins found the Takata-Ara reaction positive in 6 of 14 cases. Youmans and Warfield[28] found the reaction to the bilirubin test positive in 7 of 12 cases and the reaction to the dye test positive in 22 of 44 cases; in 4 of the 5 cases in which death occurred in this group hepatic damage was exhibited at postmortem examination. They noted no relation except loss of

27. Maes, U.; Boyce, F. F., and McFetridge, E. M.: Hyperthyroidism in the Negro, with Analysis of Seventy-Three Cases, West. J. Surg. **42**:456-463 (Aug.) 1934; Clinical Problems of Thyroid Disease in Non-Endemic Area, Am. J. Surg. **24**:232-253 (May) 1934; Further Observations on Thyroid Disease in a Non-Endemic Area: An Analysis of Six Hundred and Sixty-Two Surgical Cases and Sixteen Non-Surgical Deaths, Ann. Surg. **105**:700-716 (May) 1937.

28. Youmans, J. B., and Warfield, L. M.: Liver Injury in Thyrotoxicosis as Evidenced by Decreased Functional Efficiency, Arch. Int. Med. **37**:1-17 (Jan.) 1926.

weight between the functional efficiency of the liver and the clinical picture; other tests employed, including that for the basal metabolic rate, also furnished no parallels. They noted that evidence of hepatic dysfunction was most apt to be found in patients who in addition to loss of weight showed inability to maintain a satisfactory caloric intake.

Maddock, Coller and Pedersen [29] used the bromsulphthalein test in 13 cases of toxic goiter and found an impairment of hepatic function in 8. They noted a considerable degree of correlation between the severity of the disease, the basal metabolic rate and the degree of hepatic damage. They also found the bilirubin test satisfactory for this purpose. In their postoperative study of hepatic function they noted a gradual return to normal levels after the initial postoperative fall, but there was no correlation between the preoperative hepatic function and the postoperative course.

Hurxthal [30] studied 505 patients with thyroid disease by the cholesterol test. He found the values low in toxic states, elevated by the proper preoperative preparation and elevated most of all by operation. The lowest average values were for patients in or near crisis, and the next lowest, for patients with auricular fibrillation. The average values were lower with all types of exophthalmic goiter than with the nodular toxic varieties, and the values in cases of recurrent hyperthyroidism were almost as low. The average value for patients with the nontoxic condition was normal, although the scatter was wider than had been expected, which has been our experience with the Quick test. The level of the blood cholesterol and the basal metabolic rate showed an average reciprocal relationship. Adler and Lemmel (quoted by Lichtman [31]) noted abnormal cholesterol ester values in a few cases of severe exophthalmic goiter, finding the ester fraction depressed, as it tends to be with hepatic damage of other origins. Parhon and Cahane,[32] studying experimental hyperthyroidism, noted a tendency toward the increase of hepatic chlorides in the experimental subjects as compared with the controls.

Althausen and Wever [33] studied 26 hyperthyroid subjects by the galactose tolerance test and found the curve much higher than for

29. Maddock, W. G.; Coller, F. A., and Pedersen, S.: Thyroid Crisis: Its Relation to Liver Function and Adrenalin, West. J. Surg. **44**:513-521 (Sept.) 1936.

30. Hurxthal, L. M.: Blood Cholesterol in Thyroid Disease: II. Effect of Treatment, Arch. Int. Med. **52**:86-95 (July) 1933.

31. Lichtman, S. S.: Liver Function in Hyperthyroidism, Arch. Int. Med. **50**:721-729 (Nov.) 1932.

32. Parhon, C. I., and Cahane, M.: Sur le chlore hépatique chez les animaux hyperthyroïdesés, Compt. rend. Soc. de biol. **120**:52-53 (May) 1935.

33. Althausen, T. L., and Wever, G. K.: Galactose Tolerance in Hyperthyroidism, J. Clin. Investigation **16**:257-259 (March) 1937.

normal patients; only 2 of the maximum readings were below 30 mg. The high curve, they theorized, may be due to accelerated intestinal absorption of galactose, as evidenced by the earlier appearance of galactose in the blood, but the reduced capacity to utilize carbohydrate is undoubtedly due to hepatic injury. They refused to believe that it is dependent on the low glycogen content of the liver, as most of the 14 patients with diabetes whom they studied at the same time had normal galactose curves, although such subjects usually exhibit low values for hepatic glycogen. They did not find the changes in the galactose tolerance generally proportionate to the severity of the disease. Kugelmann (cited by Lichtman) found evidence of hepatic dysfunction in 10 cases studied by the levulose tolerance test.

Lichtman himself employed in 20 cases of uncomplicated hyperthyroidism the cinchophen test devised by himself and commented on in our first communication. Abnormal values were demonstrated in 16 cases, but there was no relation between the basal metabolic rate, the known duration of the disease and the loss of weight. He noted a tendency of the hepatic function to improve as the basal metabolic rate approached normal levels, but he did not find any appreciable correlation between his results with the cinchophen test, and the icteric index or the results of the galactose tolerance test, the bilirubin test or the urobilinogen test.

Schneider [34] has suggested that a determination of the sodium content of the blood serum will furnish an index of hepatic damage. The level is relatively constant, the norm being 281 mg. per hundred cubic centimeters. Patients with hyperthyroidism exhibit a fall in values, and operation cannot be undertaken in the presence of a level of 100 or less without grave risk. The spread seems, on the surface, rather too wide for absolute safety, and without further and stronger proof one is inclined to question his statement that the use of vitamin A will combat the fall in the glycogen content of the liver and in the sodium content of the blood serum so adequately that iodine can be dispensed with.

The tests which we have listed, most of which we described in our first communication, dealing with biliary disease, are open to precisely the same objections in thyroid disease as in biliary disease. The tests which are simple are not accurate, the tests which are accurate are usually complicated or expensive, many require repeated venipuncture, and many put an additional strain on a liver in which damage is already suspected or known to exist.

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34. Schneider, E.: Concerning Broadening of Indications for Operation in Exophthalmic Goiter Through Recognition at Bedside of Secondary Thyrogenic Injury to Liver, Internat. Clin. **2**:87-98 (June) 1934.

QUICK HIPPURIC ACID TEST OF LIVER FUNCTION IN DISEASE OF THE THYROID

In December 1936 before the Southern Surgical Association we mentioned in a report of 321 additional cases of thyroid disease from the New Orleans Charity Hospital our preliminary studies with the Quick hippuric acid test and our conviction of its value in such cases. The paper was discussed by F. H. Lahey, who said that he also had used the test for this purpose [35] and had been impressed with its reliability, though he agreed with us, of course, that it could not take the place of judgment and experience in the selection of patients adequately prepared for operation.

The test has been mentioned by several writers as suitable for use in cases of thyroid disease, but we have seen only two reports in addition to our own preliminary statement. Shorr, Richardson and Wolff [36] used it in 6 cases of exophthalmic goiter, in all of which normal values were revealed. Without intending any implication as to its correctness in these particular cases, we might point out that many times normal values are to be expected, just as normal values are to be expected in any test for any condition. The mere fact that hepatic dysfunction sometimes occurs in association with thyroid disease does not mean that it must always occur.

The only extensive report which has appeared is by Bartels,[37] from the Lahey Clinic, and is an analysis of 66 cases of toxic thyroid disease studied by the Quick test. His conclusions follow: The results of the test show that liver function in the presence of hyperthyroidism undergoes a more frequent and more intense change than has previously been suspected. The changes in function correspond to the hepatic changes demonstrated pathologically and furnish an ample basis of explanation for thyroid crisis. The degree of dysfunction is related to the clinical severity of the disease and to the degree of toxicity as indicated by the basal metabolic rate and by the necessity for operation in stages. Improvement in function occurred with preoperative preparation and was more marked in diffuse toxic disease than in nodular toxic disease; the test therefore furnishes an evaluation of the success of preoperative treatment. A postoperative decrease occurred in most cases, with a later return to approximately normal. There was no correlation between

35. Lahey, F. H.: Critical Thyroid States: Their Diagnosis and Treatment, S. Clin. North America **16**:1521-1531 (Dec.) 1936.

36. Shorr, E.; Richardson, H. B., and Wolff, H. G.: Endogenous Glycine Formation in Myopathies and Graves' Disease, Proc. Soc. Exper. Biol. & Med. **31**:207-209 (Nov.) 1933.

37. Bartels, E. C., and Perkin, H. J.: Liver Function in Hyperthyroidism as Determined by the Hippuric Acid Test, New England J. Med. **216**:1051-1060 (June 17) 1937.

the hepatic function as demonstrated by this test and the duration of the disease or the amount of weight lost, though there was a rather close correlation between it and the increase in the cholesterol content of the blood during the preoperative preparation.

The majority of the points Bartels makes we made before the Southern Surgical Association. This test, as we pointed out at that time, is a simple method which needs no elaborate facilities or special competence. It eliminates the human equation, which invalidates determinations of the basal metabolic rate for nervous and restless subjects. It puts practically no strain on the patient and therefore can be repeated as often as necessary. On the other hand, as Bayley has pointed out in his fine study of thyroid crisis, the use of such measures as roentgen examination, venipuncture and even the basal determination of the metabolic rate may at times, however necessary they may be, precipitate a serious or a fatal crisis.

We have now used this test in a sufficiently large series of cases to make rather positive statements about it, provided, of course, it is performed with the precautions set forth in our first communication. The most important, we think, is its serial use. We believe that we can now say with a fairly high degree of accuracy that one patient is a good risk from the hepatic standpoint and another a doubtful one. By repeated tests we believe that we can safely say at the end of the planned preparation that the patient has become a good risk from the hepatic aspect, or has become a fair one, or remains a poor one and must be further prepared in anticipation of the drop in hepatic function which follows any surgical procedure. We have no doubt that in this postoperative drop lies the explanation of many deaths, particularly of improperly prepared patients, which have hitherto been attributed to other causes. We hope with further experience to be able to determine the lower limits of safety, so that we may say that some patients no matter how urgently they need surgical treatment had best be left untouched, since their lack of response to preparation presages a postoperative fall in function that is likely to be more than their badly damaged livers can endure.

We pointed out in our 1936 communication, and we would reiterate with equal emphasis here, that more should not be read into this test than it can tell. It interprets hepatic damage in terms of function; repeated tests indicate alterations in function; but a single test and repeated tests tell nothing else. This is not an index of the type of risk represented by the patient with thyrocardiac disease, for whom the cardiac damage wrought by the hyperthyroidism is the outstanding consideration. This test is no index of possible respiratory failure or of any other complication except hepatic damage. These points we shall prove later by illustrative cases.

We have to date used this test in 108 cases of surgical thyroid disease, 93 of which are shown graphically (chart 1). We also have incomplete data on 39 other cases, in many of which the patients were treated surgically. The cases shown graphically are divided as follows: diffuse goiter, 26 cases; toxic diffuse goiter, 23 cases; nodular goiter, 32 cases; nodular toxic goiter, 12 cases. The percentages of normal hepatic function are shown in the accompanying table.

The conclusions to be drawn from these figures are rather surprising. It will be noted that the response to preparation of patients with nodular toxic disease was more marked than that of patients with the toxic diffuse variety. This is the reverse of Bartels' experience and perhaps is to be explained by the difference between the varieties of thyroid

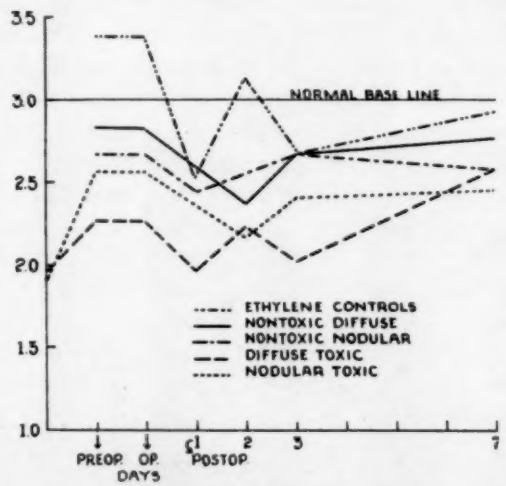

Chart 1.—Preoperative and postoperative results of the Quick hippuric acid liver function test in cases of surgical thyroid disease.

Percentages of Normal Hepatic Function

Type	Preoperative		Postoperative (by Days)			
	1	2†	1	2	3	7
Diffuse	83.0	....	52.7	70.2	79.0	81.5
Toxic diffuse	58.0	66.7	58.0	68.1	59.0	76.0
Nodular	78.8	....	71.8	74.0	79.0	76.0
Toxic nodular	57.7	76.0	69.6	64.0	71.0	72.0
Ethylene* control	100.0	....	79.0	91.0	....	88.5

* All thyroid operations are done under ethylene anesthesia on this service.
† After preparation.

disease in endemic and nonendemic areas. It may also be that our preparation was more intensive for the group with nodular toxic disease, which is largely composed of older Negroes, with whom we have

learned to fear trouble. The initial readings for both varieties of toxic disease are practically the same.

The marked fall immediately after operation, which parallels the fall in the control ethylene group (composed of young, normal persons submitted to elective appendectomy or hernioplasty) is as notable as the similar fall after biliary operations. The seriousness of the drop was always offset in the patients with toxic disease, and usually in those with the nodular type, who were older, by the use of infusions of dextrose. It is usually easy to determine from the figures the day on which the dextrose was withdrawn. For the simple diffuse type of goiter, dextrose was used only on special indications, and there was nothing to bolster the postoperative fall.

The relatively low values for the patients with nontoxic involvement suggests that this test may reveal a latent toxicity during which metabolism is increased and hepatic function correspondingly diminished, even though clinical manifestations are lacking. We wonder whether some such explanation does not hold for the rather marked difference in liver function between Negro and white patients (chart 2). Except in the group with toxic diffuse disease, the hepatic function at admission in terms of normal was invariably lower for the Negro than for the white patient:

Type	White	Negro
Diffuse	91.0	77.5
Toxic diffuse	55.6	59.0
Nodular	81.0	78.1
Toxic nodular	64.7	54.6

We are inclined to think that these discrepancies are something more than coincidence. In previous communications dealing with thyroid disease in this area we have commented that the Negro exhibits a rather low toxicity and is inclined to ignore his toxic symptoms, so that the duration of his disease is longer on the average than is the duration of the illness for white patients. This is not a particularly satisfactory explanation. Another curious fact is that Negro girls between 10 and 15 years of age exhibit both a relatively and an absolutely lower function, regardless of the nature of their disease, thyroid or nonthyroid, than do white girls of the same age.

In the occasional case we found a high hepatic function in the face of clinical evidence of extreme hyperthyroidism. As we have already said, our interest in dysfunction of the liver in the presence of thyroid disease does not blind us to the fact that it is not present in all cases. Again, it is possible that the anomaly may be explained by an excessive use of carbohydrates or of pure dextrose immediately before the test was performed. It may also be, as Chiray (cited by Youmans and Warfield) has suggested, that the first response of the liver to injury

may be an increase in functional efficiency. This holds true for hepatic cirrhosis and other hepatic states and may be true here also.

The practical application of the knowledge concerning the hepatic factor in thyroid disease has been demonstrated by Frazier and his associates, Brown, Frieman and North,[38] who have stressed the value of intravenous dextrose therapy as a prophylaxis against the violent postoperative reactions frequently seen in patients suffering from hyperthyroidism. In 70 gravely ill patients for whom they employed this therapy there were no crises and no reactions approaching crises; there

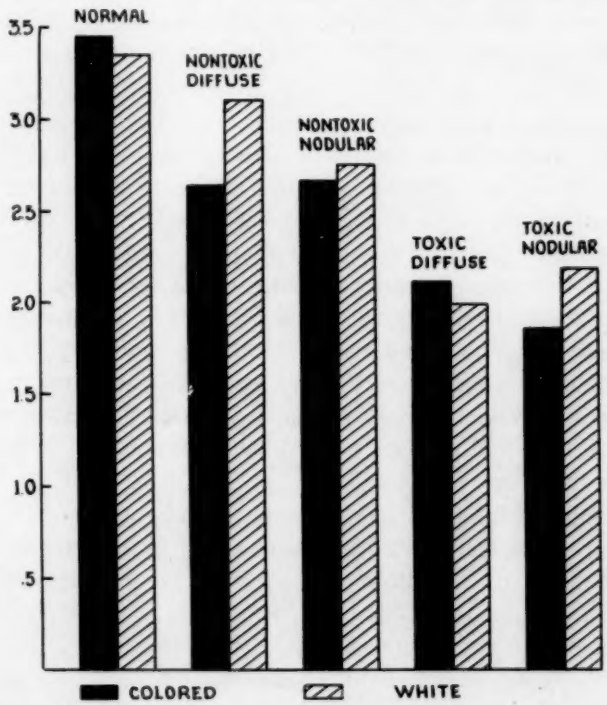

Chart 2.—Comparative study of liver function in the presence of thyroid disease, as shown by the Quick hippuric acid test performed on patients of the white and Negro races.

were also no deaths. Among a control series of 100 similar patients for whom dextrose was not used there were 2 deaths in crises, and a third patient had a similar but somewhat atypical reaction.

38. Frazier, C. H., and Brown, R. B.: The Thyroid and the Liver, Tr. Am. A. Study Goiter, 1935, pp. 168-178. Frazier, W. D., and Frieman, H.: Alterations in Liver Glycogen Following Thyroid, Iodine and Glucose Feedings, Surg., Gynec. & Obst. **60**:27-29 (Jan.) 1935. Frazier, C. H., and North, J. P.: Carbohydrate Metabolism in Hyperthyroidism, Tr. Am. A. Study Goiter, 1933, pp. 203-209.

These same authors have stressed another important consideration, that the fatty changes frequently found in the livers of patients with hyperthyroidism are likely to be just as serious as the depletion of the hepatic glycogen, on which we have tended to focus our entire attention in the past. A high carbohydrate diet and the liberal use of dextrose will take care of the glycogen depletion, but other measures are needed to protect the organism against the equally serious fatty changes in the liver. If repeated determinations of blood sugar show that the dextrose is not being absorbed, lecithin should be added to the therapy. The persistent hypoglycemia in a case reported by Kramer and his associates and mentioned in our first communication could be explained on the basis of fatty changes in the liver, and it is possible that a similar explanation would hold in many cases of thyroid disease.

It is our own strong conviction that a large part of the decrease in the mortality from thyroid disease in Charity Hospital in 1936 as compared with the figures reported in 1933 is due to the use of dextrose in the second series. In the first 341 cases there were 26 deaths, 7.6 per cent, against 12, or 3.7 per cent, in the second 321 cases. In the first series there were 19 deaths in 177 cases of toxic disease, 10.8 per cent, against 8 deaths in the second series of 121 cases, 6.6 per cent. In the second series dextrose was used almost routinely as a postoperative measure in cases of the toxic type, as well as in many instances of nontoxic involvement. Rarely was it withheld until the need for it was demonstrated, and perhaps a still more liberal use of it would have reduced the mortality further.

The postoperative use of oxygen might also be a means of reducing the mortality caused by the hepatic factor. Judd [39] noted that the oxygen saturation of the blood is decreased in patients with hepatic disease and suggested inhalations of oxygen as a corrective measure. His conclusion that perhaps one result of transfusion is to improve the oxygen saturation curve seems entirely rational, and both oxygen therapy and transfusion would seem indicated for toxic thyroid disease in which the hepatic factor is apparent.

The following cases present several points of interest.

CASE 1.—An exceedingly toxic Negro aged 37 entered the hospital with congestive heart failure and a two year history of toxic (diffuse) thyroid disease. Preparation for surgical treatment was complicated by the necessity for thoracentesis and the extreme difficulty of keeping him in bed and submissive to the regimen ordered for him. At the time of his admission the Quick test reading was 1.221, approximately 35 per cent of normal. Before the first lobectomy, for which he was prepared by standard treatment (including dextrose therapy) the value had risen to 2.523. He stood the operation well; he was given dextrose

39. Judd, E. S.; Snell, A. M., and Hoerner, M. T.: Transfusion for Jaundiced Patients, J. A. M. A. **105**:1653-1658 (Nov. 23) 1935.

liberally for several days afterward, and after the expected postoperative drop the test of hepatic function showed almost the same reading as before. Because his cardiac condition made him a very poor risk, the second operation was delayed as long as possible, but the recurrence of the toxic symptoms, together with evidence of failing hepatic function by serial Quick tests, clearly indicated the necessity for the second lobectomy.

He was prepared for it with even more difficulty than for the first, partly because of the confusion incident to the demolition of the old Charity Hospital and the removal of the patients to other quarters. Then, two days before operation was to be done, through a most unfortunate error he was dismissed from the ward by a house officer charged with the task of clearing the hospital of all patients except those in urgent need of treatment, during the actual days of moving. The error was promptly discovered, and the patient was brought back to the hospital from the country four days later. He was in very poor condition, however, especially from the cardiac aspect. Again he was prepared for operation, and when this was undertaken ten days after his return, his hepatic function, which had fallen to 1.461 during his absence from the hospital, had risen to 2.974, though the cardiac state was extremely unsatisfactory. His immediate reaction from the second lobectomy was not alarming, but congestive cardiac failure developed on the second day, and he died within forty-eight hours. Permission for autopsy could not be secured. We have quoted this case at length because it illustrates two points. The first is the correlation between clinical improvement and regression and the elevation and fall in the Quick test readings. The second is the uselessness of the test as an indication of cardiac risk.

CASE 2.—A Negress aged 36 was admitted to the hospital with typical symptoms of nodular toxic goiter. She had been treated with iodine for an undetermined period before admission. In her first test of hepatic function the reading was 1.950, and in the second, five days later, 1.114, the decrease corresponding to the extremely nervous state to which she had been reduced by the noise and confusion incident to the demolition of the hospital. During intensive preparation of the patient for the operation the function rose to 2.789, and she seemed so good a risk that subtotal thyroidectomy was done instead of the lobectomy which had been originally planned. She reacted well. Three hours later, just as an intravenous infusion of dextrose was about to be given, with a normal blood pressure, a pulse rate of 90, a temperature of 99 F. and a respiratory rate of 22, she suddenly stopped breathing and could not be revived. The patient was under observation when the catastrophe occurred. There was no evidence of hemorrhage, nor could any other accident be demonstrated as a possible cause of death. Autopsy was not permitted. The hepatic factor clearly played no part in this death, and, again, such a fatality cannot be predicted by the Quick or by any other test for hepatic function.

CASE 3.—A white woman aged 43 was admitted to the hospital with a toxic nodular goiter and signs of extreme toxicity. The initial hepatic function of 1.859 rose to 3.425 after intensive preparation, including dextrose therapy. Operation was done in stages, in spite of the improvement. The hepatic function after operation was well maintained until the fourth day, when dextrose was withdrawn. Then it fell to 1.796, although it rose gradually thereafter, and convalescence was without incident. She returned for the second operation two months later, at which time the initial hepatic function was 3.012 and her clinical condition was greatly improved. After proper preparation the second lobectomy

was done, without complications. Again the tests of hepatic function, after the initial postoperative drop and the further drop when dextrose was withdrawn, kept pace with the clinical improvement.

This case furnishes an excellent illustration of the value of the test as an index of the efficacy of preoperative preparation, as well as of the improvement in function which follows properly performed operations. Clinically the patient on admission was a very poor risk.

SUMMARY

Clinical and experimental proof of the relation between the liver and the thyroid is presented.

The tests of hepatic function previously used in thyroid disease are discussed.

Our own experience with the Quick hippuric acid test of hepatic function as applied to thyroid disease is outlined.

The conclusions possible from our results are discussed.

Illustrative cases are cited.

STUDIES OF HEPATIC FUNCTION BY THE QUICK HIPPURIC ACID TEST

III. VARIOUS SURGICAL STATES

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AND

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NEW ORLEANS

In two previous communications [1] we have discussed the value of the Quick hippuric acid test of hepatic function in the treatment of hepatic and biliary disease and of thyroid disease. In this communication we shall consider it in connection with the general problems of surgery. We are increasingly of the opinion that the role of the liver in all types of surgical disease is more important than is generally suspected, and we are in hearty accord with the writers—they are relatively few—who make the point that it is quite as important to consider the liver in evaluating the surgical risk as it is to consider the heart, the kidneys and the lungs.

In our first paper on the subject of "liver death," which was written in 1934, we said:

> Our experimental study has not yet progressed to the point at which we feel that we can make suggestions of any value to prevent the distressing catastrophe of "liver death." The most important consideration, it seems to us, lies in Graham's rather casually uttered statement that . . . the patient with a damaged liver presents a questionable risk not only for operation on the biliary tract, but for any operation, no matter how trivial it may be . . . that warning, taken at its face value, will mean for all practical purposes a surgical revolution. It will mean that there will be no more "simple surgery." It will mean, particularly, that the surgeon who proposes to perform operations on the biliary tract . . . must regard all such patients as presenting potentially poor risks, regardless of how incongruous their inclusion in such a category may seem. It means, to go further, that all candidates for any operation must be studied from the standpoint of hepatic function, and that the ninety and nine must be discommoded and inconvenienced to rescue the one who may otherwise be lost.

From the Department of Surgery of the School of Medicine of Louisiana State University, and the Charity Hospital of Louisiana.

1. Boyce, F. F., and McFetridge, E. M.: Studies in Liver Function by the Quick Hippuric Acid Test: I. Biliary and Hepatic Disease, Arch. Surg., this issue, p. 401; Studies in Liver Function by the Quick Hippuric Acid Test: II. Thyroid Disease, ibid., this issue, p. 427. These papers contain extensive lists of references, which are not repeated here.

When those words were written we were unaware of Shallow's statement to the same effect, though actually, as Robertson pointed out, he seems to have been one of the very first to be emphatic about the matter. In the course of a staff meeting he mentioned a certain unexpected mortality in his surgical practice, the reason for which became clear when dye retention tests for hepatic function revealed in many cases damage of which there had been no clinical evidence. In the light of those findings he adopted the principle that patients who reveal such damage and who do not respond to standard measures to correct it had best be refused all but emergency operations.

The data on patients whom we have studied as controls in our work with the Quick hippuric acid test bear out Shallow's contention. For most of the 28 presumably normal patients whom we studied the test readings were normal, as were those for the normal subjects studied by Vaccaro, Quick, Kohlstaedt and Helmer, and Yardumian and Rosenthal. Yet at intervals we found patients normal by every clinical standard who revealed unexpectedly low values in this test. Such patients we are inclined to look on with dubious eyes unless they are definitely prepared for their surgical ordeal, for our controls show that even entirely normal persons undergo a more or less marked drop under all types of anesthesia.

Knowledge of the effect of anesthesia on the liver is, of course, not new. The work of Rosenthal [2] and of Bourne,[3] to mention only one group of workers in this field, has made it clear that ether as well as chloroform causes an impairment of hepatic function as measured by the dye test. Bourne wrote:

> The striking difference between the ether and chloroform results is that with the former the animal has returned to normal the next day, while with chloroform the harm continues to progress, and does not reach a maximum until the day after the anesthesia.

Our findings are also more striking than those of Cantarow, Gartman and Ricchiuti.[4] Studying 60 patients on whom cholecystectomy was performed for biliary disease without jaundice, they found by the bilirubin and the dye retention test evidence of postoperative impairment of hepatic function, which sometimes lasted four days.

Our findings with the Quick test, as we have said, are rather more striking. For purposes of comparison with our groups of patients operated on for disease of the thyroid gland or of the biliary tract, we

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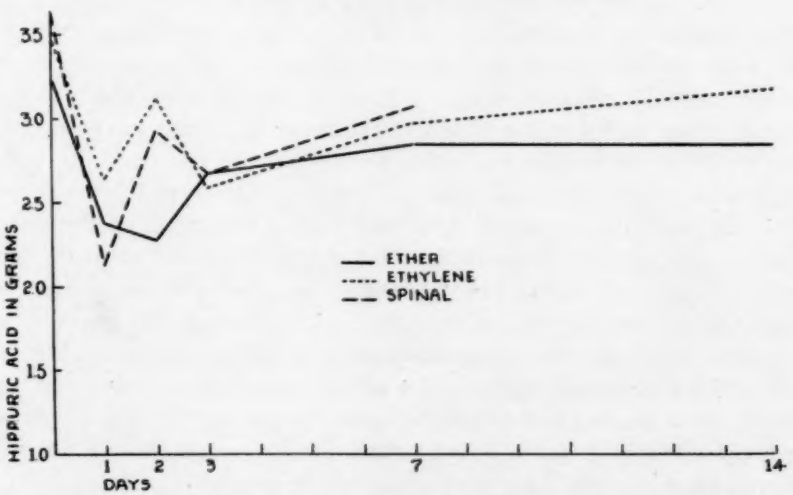
2. Rosenthal, S. M., and Bourne, W.: The Effect of Anesthetics on Hepatic Function, J. A. M. A. **90**:377-379 (Feb. 4) 1928.

3. Bourne, W.: Anesthetics and Liver Function, Am. J. Surg. **34**:486-495 (Dec.) 1936.

4. Cantarow, A.; Gartman, E., and Ricchiuti, G.: Hepatic Function, Arch. Surg. **30**:865-874 (May) 1935.

elected to study as controls (see chart) groups of presumably normal persons who were to undergo elective operations (appendectomy and hernioplasty) for conditions not connected with the biliary tract or the thyroid gland, in order to note the effect on hepatic function of supposedly simple operations. These patients were not specially prepared for operation, nor were they given special postoperative treatment; only patients who made an uneventful convalescence were included. It is interesting and surprising, as we have implied in previous communications, to note what anesthesia and simple operations do to the liver, as expressed in percentages of normal function (table 1).



Preoperative and postoperative results of the Quick hippuric acid test for liver function in uncomplicated appendectomies and hernioplasties performed with various types of anesthesia.

TABLE 1.—*Percentage of Normal Function*

Anesthetic	Admission	Postoperative (by Days)				
		1	2	3	7	14
Ethylene	100	79	91.0	....	88.5	....
Ether	95	70	67.4	79.3	83.4	83.4
Spinal	111	62	87.0	79.0	90.1	92.0

On the basis of these figures, the Quick test would seem to be a more delicate index of hepatic function than either the bilirubin test or the dye test, which were used in the studies just referred to.

There are many possible explanations for the 25 per cent drop in hepatic function with ether anesthesia. Crile, for instance, showed the serious consequences of exposure of the liver during abdominal

operations and said that the deleterious effects are enhanced when ether anesthesia is used. With each degree of falling temperature, he stated, there is a loss of 10 per cent in hepatic efficiency. He suggested the use of diathermy during operation as well as during the critical days after the operation, to take care of the thermal factor. He also suggested that a less dangerous anesthetic than ether be used.

Mann and his associates have shown that the hyperglycemia which occurs after ether anesthesia is the result of a loss of glycogen from the liver. Mann has also shown that ether decreases secretion of bile and depresses other hepatic functions, notably the formation of urea.

From another standpoint, Bourne's experiments have shown that when inhalation anesthetics, even such safe ones as nitrous oxide and ethylene, are administered without adequate oxygenation the experimental animals suffer an impairment of hepatic function which requires several days to overcome. Shaw, Steele and Lamb [5] have shown in recent elaborate studies on ether anesthesia the existence of anoxic anemia and have suggested that oxygen be administered coincidentally with the anesthetic to secure a normal oxygen saturation of the arterial blood. The work of Goldschmidt, Ravdin and Lucke [6] is to the same purpose. By volatilizing the anesthetic with oxygen they were able largely to prevent the necrotizing effect on the hepatic cells usually produced by such an agent as chloroform or divinyl ether. They also found that a high carbohydrate diet before operation had much the same effect. Their theory, based on experimental evidence, is that the improvement which occurs in the portal circulation as the result of inadequate oxygenation may play an important part in the result. This would be in line with Judd's idea, which we have mentioned in our earlier communications, that hepatic dysfunction is associated with defective oxygenation of the blood.

It must be remembered that these normal patients, even though they are not formally prepared for operation, do undergo a period of starvation or semistarvation, sometimes for as long as twelve or fourteen hours. The work of C. S. Stone, which we mentioned in our first paper on the Quick test, is applicable here. Working with partially hepatectomized rats which had been fed a high carbohydrate diet, he found that if the animals were killed when the stomach was full the glycogen level was high, whereas if they were killed when the stomach

5. Shaw, J. L.; Steele, B. F., and Lamb, C. A.: Effect of Anesthesia on the Blood Oxygen, Arch. Surg. **35**:1-10 (July) 1937.

6. Goldschmidt, S.; Ravdin, I. S., and Lucke, B.: Anesthesia and Liver Damage: I. The Protective Action of Oxygen Against the Necrotizing Effect of Certain Anesthetics on the Liver, J. Pharmacol. & Exper. Therap. **59**:1-14 (Jan.) 1936.

was empty the hepatic glycogen values were low. The early experiments of Whipple and his associates on hepatic damage produced by chloroform showed that the full effect of the anesthetic on the liver could not be felt unless the animals were starved before its administration. In recent (unpublished) experiments of our own we have duplicated these findings and have been impressed with the prompter and more extensive damage produced in the liver when the chloroform was given to starved animals. Unquestionably the administration of the anesthetic after the period of starvation plays some part in the drop in hepatic function after operation.

It is a striking fact that although the patients operated on under spinal analgesia showed the highest initial values—all of them were young, vigorous men—they also showed the greatest postoperative fall, 49 per cent. For most of them the operation performed was hernioplasty, which does not involve extensive exposure of the abdominal contents, or appendectomy through a McBurney incision, of which the same may be said.

There are many explanations for this drop, some of them probable, some of them purely speculative. It is reasonable to assume that the fall in blood pressure which is known to occur with spinal analgesia may result in a decreased oxygen supply to the liver. If this is so, it is entirely possible that the postoperative decrease in hepatic function is at least partly due to an anoxemia, exactly as with inhalation anesthesia, in connection with which we have already pointed out the results of inadequate oxygenation.

Another explanation of the postoperative drop after spinal analgesia is perhaps found in the fact that the drugs used to secure it, like the drugs used to secure local analgesia, are largely eliminated in the liver. Heyd noted that anesthetics given by rectum or by colon are eliminated in the same way; he warned against using them and adding further insults to the liver when hepatic damage is known or suspected to exist. He too stated that nitrous oxide or ethylene with the addition of very small amounts of ether is the safest of all anesthetics.

The dangerous possibilities inherent in spinal analgesia have long been realized, and our findings in this test make those risks doubly impressive. A recent study by Veal and Van Werden [7] from Charity Hospital may be quoted in this connection. In a study of 30 fatalities directly attributable to spinal analgesia they found that 19 of the deaths occurred in the presence of such abdominal conditions as intestinal obstruction, peritonitis, gunshot wounds, hepatic abscess and cholecystitis.

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7. Veal, J. R., and Van Werden, B. deK.: Mortality of Spinal Analgesia Based on an Analysis of Thirty Immediate Fatalities in a Series of 33,811 Cases, Am. J. Surg. 34: 606-610 (Dec.) 1936.

These are all conditions in the presence of which it is not unreasonable to postulate some degree of hepatic damage, particularly when one recalls the advanced stage of illness at which many patients are seen. We have no tests on these patients to prove our point, but it is not unreasonable to assume that the fall in hepatic function after the administration of the spinal analgesia may have had something to do with the fatal outcome.

In a recent study of 715 cases of acute intestinal obstruction from Charity Hospital [8] we found further indirect proof of the possible effect of spinal analgesia on the liver. In 9 of these cases hepatic damage was apparent as the only cause of death, and 6 of the 9 patients had had spinal analgesia. We have no tests to prove the point, but it is permissible to draw attention to what may be a coincidence but may also be a cause and effect relation. We suggest that the same fall in hepatic function noted in healthy subjects after operation and withstood by them might have occurred with disastrous results in patients with intestinal obstruction whose livers were already damaged—there is no doubt of that damage in certain cases of obstruction. All these patients died promptly, with hyperpyrexia or with uremic symptoms typical of "liver death" or the "liver-kidney syndrome." Whether or not our presumptions are sound, we are certainly justified in saying that spinal analgesia is not the safe anesthetic it is usually supposed to be. If ethylene could give the proper relaxation it would seem to be the safest anesthetic of all. We have had no experience with cyclopropane, but in view of the high admixture of oxygen which it permits, it would also seem a very safe agent.

It is regrettable that the Quick test is not applicable to patients with intestinal obstruction, for it should furnish some interesting results. Such patients, of course, cannot safely be given fluids by mouth, nor can they be deprived of fluids by other routes for the period necessary to the test. Del Rosso [9] reported 7 cases of intestinal obstruction studied by the rose bengal test, in all of which there was a high retention of the dye, and we regret that we cannot duplicate his studies with the Quick test.

In connection with our studies in anesthesia we report an interesting case:

A young and vigorous man, 18 years old, was operated on in July 1937 for an indirect inguinal hernia on the left side. It was causing no symptoms, but

8. Boyce, F. F., and McFetridge, E. M.: Acute Intestinal Obstruction, South. Surgeon **6**:109-125 (April) 1937.

9. del Rosso, L. M.: La funzionalità epatica, nell'occlusione intestinale acuta, studiata con il rosa bengala (Contributo clinico e sperimentale), Policlinico (sez. chir.) **40**:224-236 (April) 1933.

he had been refused admission to a CCC camp until it was corrected. The routine tests and the urea clearance test gave normal values. Operation was done under ethylene anesthesia and took forty minutes. The preoperative hepatic function was 3.726; on the first day after the operation it was 2.801 and on the fourteenth 3.222.

The patient was readmitted to the hospital at the end of September with a story of several recurrent attacks of appendicitis during the interval. We were not aware of the readmission, and the Quick test was ordered by the intern without our knowledge, because, as he told us, the man had so many complaints he thought he would furnish him with something to complain about. It was well that he had this inspiration, for the studies on this patient were most interesting. The value on admission was practically what it had been on his discharge ten weeks before, 3.205. Appendectomy was done with the patient under ether anesthesia, through a right rectus incision, and took forty-five minutes; the appendix was retrocecal and contained one fecalith. On the first day after the operation the patient was perfectly well; he had not vomited; there was no distention; the temperature, the pulse rate and the respiratory rate were within normal limits, but the hepatic function value had fallen to 1.891. On the fifth day it had risen to 2.449 and on the seventh to 3.022. The marked difference between the values revealed by the Quick test after the use of different anesthetics and after different procedures is so obvious as to need no comment.

Another interesting problem is furnished by an 80 year old patient who was submitted to hernioplasty and orchidectomy. Routine laboratory tests showed normal values, as did the urea clearance test, and the Quick test showed a reading of 2.9. In spite of the excellent hepatic function, we suggested that because of the patient's age ethylene be used for the operation. On the first day after the operation the Quick test was 2.035, and it had reached only 2.434 on the seventh. It is interesting to speculate what the postoperative drop might have been for this aged subject had ether or spinal anesthesia been used.

The lesson to be derived from these observations is clear. Even elective operations on sound subjects result in an impairment of hepatic function, against which it might be well to guard by such simple measures as the oral administration of carbohydrates, particularly dextrose, before and immediately after operation. We have previously quoted the work of Althausen to show the efficacy of dextrose administered by this route. It seems particularly wise to do this as a matter of routine because of the occasional unexpected death which follows even elective operations on supposedly sound persons. A recent death in our own service illustrates this point:

A Negress aged 19 was operated on under ether anesthesia for recurrent appendicitis. The appendix was retrocecal and rather difficult to remove. It was noted that the patient did not recover well from the anesthetic, remaining drowsy and listless most of the day. The following morning she seemed better, but thirty-one hours after operation the temperature began to rise, and she died six hours later, with an axillary temperature of 105.6 F. She did not respond

to infusions of dextrose. Permission for autopsy was refused, but there was no clinical evidence of shock, hemorrhage or anything else to explain why she died. Perhaps a preoperative study of the hepatic function might have revealed an unexpected deficiency, and steps could have been taken to guard against the catastrophe.

Some of the other cases (some 40 in all) which we have studied by this test are set forth in table 2 and need only casual comment. Not much work, so far as we can determine, has been done with hepatic function tests in cases of splenic disease. Greene and his associates, who used the dye test, considered it of value in relation to the severity of cirrhotic changes in the liver and therefore of some value prognostically and diagnostically. Most of the other tests they employed gave negative results, and they considered the bilirubin test of value as an index rather of the severity of the hemolytic process than of hepatic impairment.

In both cases of carcinoma of the pancreas reported by Quick, the hepatic function was less than 50 per cent of normal. In all our 6 cases the function was reduced, in some instances to 20 per cent or less of normal values. One case (case 6) bears out our repeated contention of the value of dextrose. We reported the patient safe for operation, and after intensive preoperative preparation with both oral and intravenous use of dextrose, cholecystenterostomy was performed, from which, in spite of his age (70 years), he made an excellent recovery. Dextrose therapy was continued intensively for eight days after operation, and the hepatic function was actually higher on the seventh day after the operation than it had been before operation. Both subsequent tests showed a considerable drop, unquestionably, we believe, because the intensive dextrose therapy was withdrawn and the full effect of the operation was felt.

The single case of benign pancreatic disease (case 11) is also interesting, but unfortunately operation was done before we began to use the test serially, and our studies are therefore inadequate. The patient, a Negro aged 51, was a poor surgical risk. The preoperative value for hepatic function was 1.437. Intensive dextrose therapy was given in preparation, and cholecystgastrostomy was done with the patient under ethylene anesthesia, for what was considered to be carcinoma of the head of the pancreas. The diagnosis was made chiefly on the basis of the stony hardness of the growth, although the absence of gross metastasis was commented on and was explained by the character of the disease observed at autopsy.

The patient's postoperative condition was never anything but hopeless, but it was a matter of extreme interest to us to study his urinary function in connection with the influence of decholin sodium (sodium

TABLE 2.—*Various Diseases*

No.	Race	Sex	Age	Diagnosis	Quick Test	Comment
1	White	Female	31	Banti's disease	3.025	Preoperative
					3.748	After splenectomy, 4th and 6th days
					3.443	Intensive dextrose therapy
2	White	Male	22	Banti's disease	1.168	Preoperative
					2.424	After splenectomy, 1st, 2d, 3d
					3.180	and 8th days; intensive dextrose
					2.4	therapy, withdrawn 5th day
3	White	Male	49	Banti's disease	2.129	Preoperative
					1.325	After splenectomy, 7th and 14th
					2.088	days, after dextrose had been discontinued
4	White	Male	61	Tuberculosis of spleen	2.474	Preoperative
					0.778	After exploration, 1st, 2d, 3d,
					0.935	7th and 14th days
					1.462	
					1.752	
					1.837	
5	White	Male	71	Carcinoma of head of pancreas	1.708	Preoperative; icteric index 66.6; transfusion
					1.94	Fourteen days after cholecystgastrostomy
6	Negro	Male	70	Carcinoma of head of pancreas	2.469	Preoperative; icteric index 100; dextrose preparation
					2.72	After cholecystgastrostomy, 7th
					2.017	10th and 14th days; dextrose
					1.491	withdrawn 9th day
7	White	Male	64	Carcinoma of head of pancreas	1.174	Operation refused; patient left hospital; icterus index 166
					0.429	Return 6 weeks later
					1.222	Fourteen days later; daily dextrose infusions; autopsy confirmed diagnosis
8	White	Female	45	Carcinoma of head of pancreas	0.490	Inoperable; icterus index 111
9	Negro	Male	73	Carcinoma of head of pancreas	0.716	Operation refused; icterus index 100
10	White	Male	54	Carcinoma of head of pancreas	2.413	Clinical diagnosis; operation refused
11	White	Female	69	Carcinoma of head of pancreas	0.636	Refused operation; icterus index 125
12	Negro	Male	51	Cystic disease of pancreas	1.437	Preoperative; icterus index 100
					0.812	Nineteen days after cholecystgastrostomy; liver-kidney death 10 days later; repeated improvement in uremic symptoms after decholin therapy
13	White	Male	60	Gastric carcinoma	2 286	Hepatic metastasis; exploration
14	White	Male	61	Gastric carcinoma	2.501	Hepatic metastasis; exploration; sudden death (embolic?) 23 days after operation
15	White	Male	49	Carcinoma of rectum	0.615	Preoperative
					1.407	After preparation
					0.614	1st day after colostomy
					1.057	3d day after colostomy
					0.699	Jaundice; icterus index 100
					0.522	Three weeks ante mortem; autopsy refused
16	White	Female	63	Diabetes	3.642	After stabilization
17	White	Female	63	Diabetes	1.409	Blood sugar 205
					2.172	Stabilization begun
18	White	Male	51	2d degree burns, small area	2.601	Three days after admission
					3.958	Twenty-eight days later

TABLE 2.—*Various Diseases—Continued*

No.	Race	Sex	Age	Diagnosis	Quick Test	Comment
19	White	Female	47	2d degree burns, one fourth body area	1.908 2.192 2.791	Three days after admission Four days later Three months later
20	Negro	Male	48	Multiple myeloma	1.817 1.430	
21	White	Female	44	Cardiac disease	2.835	Compensated
22	White	Male	28	Malaria	3.368	After treatment
23	White	Male	26	Urethritis	3.754	
24	Negro	Female	19	Sickle cell anemia	2.011 1.589	Two weeks later
25	White	Female	46	Dyspepsia of undetermined origin	2.540 1.980	Fourteen days after exploration under ether; negative findings
26	White	Female	69	Dermoid cyst of neck	2.193 1.990	Fourteen days after removal under ethylene, operation lasted 2 hours
27	White	Female	28	Salpingitis	3.615	

dehydrocholate) on his hepatic function. The urea content of the blood rose steadily, reaching 88 mg. per hundred cubic centimeters just before his death, but again and again when it rose to abnormally high levels and uremic symptoms appeared, injections of decholin reduced it and eliminated the symptoms temporarily. He finally died on the twenty-fifth day after operation with progressive anuria. Autopsy showed cystic disease of the pancreas, associated with a marked degeneration of the liver. In our study of the Quick test for patients with biliary disease we have discussed at length the relation between urinary output and hepatic dysfunction, and it is unfortunate that we did not make repeated tests in this case. On the other hand, the second test, performed fourteen days after operation and eleven days before death, showed much impaired hepatic function (0.812).

One of the 2 cases of carcinoma of the rectum (not listed) deserves special comment. The patient was studied at intervals for two months, during which time biopsy of material taken from the rectum was done, colostomy was performed and exploration was made in the hope that resection of the growth might be possible. All the operations were done with the patient under ether anesthesia. The initial hepatic function value was 3.140, and it was interesting to observe the fall and rise after each operation. Particularly notable was the fall of 50 per cent after the first operation, in which biopsy of material from the rectum was done but postoperative dextrose therapy was not given, as compared with the fall of only 28 per cent after the second, in which colostomy was

done and intensive postoperative dextrose therapy was instituted. The patient died three months after the third operation, and autopsy, which revealed the liver entirely free from metastasis, explained why the hepatic function had remained unimpaired.

Bargen and his associates studied by the dye test 116 cases of carcinoma of the colon and rectum, in which ascites was not present. In half the cases the presence of hepatic metastases, which they had suspected clinically, was confirmed by the evidence of hepatic impairment furnished by this test. In the other cases, although the liver was not palpable, the impaired hepatic function revealed by the test was confirmed at operation when the surgeon found the liver riddled with metastases. The direct van den Bergh reaction did not occur constantly enough in this series to be of diagnostic value. Bargen suggested that in the occasional case a test of hepatic function may reveal unsuspected metastasis and spare the patient a useless and perhaps lethal exploration. We are not yet sufficiently convinced of the accuracy of the Quick test, or of any other, to direct our therapy by its results.

We have studied hepatic function by the Quick method in 4 cases of burns. In this type of case one is handicapped by the fact that the most seriously injured persons, in whom most extensive hepatic damage would be likely to occur, cannot safely be deprived of fluids for the period necessary for the test. All of these burns were of moderate degree, but for all patients the initial test showed lowered values, the readings ranging from 2.601 for the least extensive to 0.890 for the most extensive injury. The last mentioned case (not listed) is worth reporting. The test was repeated at intervals over a period of twenty-eight days while the patient was recuperating from the burn. Convalescence was satisfactory, but on only one occasion did the value rise to 2.663; the rest of the time it did not rise above 1.8. On the twenty-eighth day she suddenly showed acute abdominal symptoms, for which operation was done ten hours later, after a diagnosis of mesenteric thrombosis had been made. Extensive resection of the small bowel was necessary. After a brief period of remarkable improvement she grew rapidly worse. She died on the tenth day after the operation. Autopsy showed localized peritonitis, which perhaps was sufficient to explain her death. On the other hand, degenerative changes were present in the liver, and the markedly impaired hepatic function may have played some part in the fatal result.

We have used the test in so few cases of pregnancy that we are unprepared to comment on it personally except to say that if the nitrogen retention in the blood is high, as it was in 2 of our cases, the Quick test must be interpreted with this fact in mind. Kohlstaedt and Helmer used the test in 5 cases of toxemia of pregnancy and found the values

generally low. Hirscheimer used it for 25 patients and found that even normal pregnant women showed an impairment of function near term. Toxic patients showed a more marked drop. In most cases normal values were reached during the puerperium. His findings corroborated the studies of Sullivan, Tew and Watson, he noted, with the bilirubin and dye tests. He pointed out also that the dietary treatment usually given for the toxemias of pregnancy may increase instead of improve the hepatic impairment and suggested as a substitute the intensive use of aminoacetic acid.

Of the miscellaneous cases we have studied, only 1 (not listed) is worth special comment. A Negress aged 45 was sent to us from the gynecologic service for the investigation of a mammary tumor following hysterectomy, convalescence from which had included a rupture of the wound, with resuture. The initial reading was 0.698, and as she refused further surgical treatment we have no other report on her. This case is to be compared with one reported in our first paper, on the group of patients submitted to operations on the biliary tract. This patient, a man aged 36, made an excellent recovery from cholecystectomy for chronic cholecystitis, except that he had a persistent cough. His hepatic function was 3.205 before operation and 2.400 on the seventh day after the operation. On the tenth day he suffered a rupture of the wound with extensive evisceration; resuture under local analgesia was done fourteen hours later. The hepatic function three days after the second operation had fallen to 1.726, though it was practically normal again when he was discharged. It will be interesting to study other cases of evisceration, to determine whether such lowered readings are accidental or are constantly associated with this complication. If they are, they may explain some of the deaths which follow it.

Kohlstaedt and Helmer suggested the Quick test as a method of evaluating the possible risk of the therapeutic use of such hepatotoxic drugs as arsphenamine. The incidence of jaundice in patients treated by this method, they pointed out, has been shown by Wile and Sams to be 1.3 per cent, against an incidence of 0.18 per cent in untreated patients. We have no complete studies on patients with this sort of condition, nor have we any on patients with arsenic poisoning, such as Heyd described. In support of his idea that retained arsenic may be a factor in hepatic degeneration he mentioned 3 patients in whom the condition was identified within a relatively brief period at the Postgraduate Hospital, all admitted for nonbiliary disease. The figures of Vogel, which he cited, showed an excess of arsenic in the secretions of 34 of 40 jaundiced patients; 9 of the 34 patients died. Heyd's theory is that the wide use of arsenic as an insecticide and in the dyeing and textile trades, as well as the presence of minute quantities

in cooking utensils and city dust, makes this possibility not as fantastic as it sounds. The Quick test might be of value in suspected cases of this sort.

SUMMARY

The results of the Quick hippuric acid test for hepatic function have been analyzed in a series of presumably normal subjects on whom simple elective operations were done, various types of anesthesia being used.

In all cases there was a marked drop in hepatic function after operation, the impairment being most marked with spinal analgesia and least marked with ethylene anesthesia.

The possible causes of this postoperative drop are discussed, and the wisdom of preparing all patients for operation, regardless of how normal they may seem and how simple the procedure may be, is pointed out.

The results of the test in a miscellaneous group of cases, including cases of intestinal obstruction, of splenic disease, of malignant tumor of the rectum, of pancreatic disease and of burns, are discussed.

Other possible uses of the Quick test are suggested.

TREATMENT OF INTRACTABLE BRONCHIAL ASTHMA BY BILATERAL RESECTION OF THE POSTERIOR PULMONARY PLEXUS

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Although it is relatively small, there exists a group of patients afflicted with typical bronchial seizures which are unamenable to medicinal therapy. It is to the amelioration of these attacks in such patients that our attention has been drawn. Only cases of unquestionable bronchial asthma have been selected, and only patients totally incapacitated physically have been subjected to operation. The rationale of the procedure of bilateral resection of the posterior pulmonary plexus is based on the anatomic fact that only at this point can the extrinsic nerve supply of the lung be completely interrupted. The preganglionic efferent fibers of both the vagus and the sympathetic bronchomotor tracts from the same and contralateral sides, together with the sensory or afferent fibers emerging from the lung, form a rather limited anastomosing plexus on the posterior surface of the hilus of the lung. By resection of this plexus it is therefore possible to isolate the entire organ from any influence brought to bear on the lung through its extrinsic nerve supply. Physiologic observations made both in the past and recently have shown beyond question that bronchoconstrictor fibers are distributed mainly in the branches of the vagus nerve to the lung of the same side and that of the opposite side and to some extent accompany the sympathetic fibers. Sensory fibers from the lung, whose ganglions are to be found mainly in the ganglion nodosum, run principally in the vagi but also to some extent in the sympathetic trunks. By various experimental methods of stimulation of the proximal and distal ends of the divided vagi and sympathetic trunks as well as of the intact nerves, pronounced narrowing of the air passages of the lungs has been produced. Further reference to this will be made.[1]

From the Surgical and Medical Clinics of the Johns Hopkins University.

1. Longet, F. A.: Anatomie und Physiologie des Nervensystems des Menschen und der Wirbeltiere, translated by J. A. Hein, Leipzig, Brockhaus & Avenarius, 1849, p. 247. Volkmann: Nervenphysiologie, Handwörterb. d. Physiol. **2**:586, 1844. Riegel, F., and Edinger, L.: Experimentelle Untersuchungen zur

(Footnote continued on next page)

The selection of patients for this method of treatment depends on the severity and frequency of the asthmatic seizures. Therefore, a most careful diagnostic survey is essential, and less radical measures should first be carried out in an attempt to relieve the patient.

Those of our patients for whom this method of treatment was used had been under observation in the asthma clinic of the Johns Hopkins Hospital for many months. They were thoroughly examined for causes of asthma, and when a suspected cause was discovered effort to relieve the patient was made by administration of the appropriate treatment. All foci of infection were removed; the patient was frequently hospitalized to tide him over a period of violent asthmatic paroxysms, and when such treatment was indicated specific antigens were given subcutaneously in an attempt to desensitize the patient to the offending agent. Only in cases in which it was felt that the recurring severe and prolonged asthmatic attacks might cause the death of the patient did we recommend operative intervention.

This report covers the treatment of 11 patients who were repeatedly in a condition of status asthmaticus before operation and who were consequently economically and socially completely incapacitated. The first patient was operated on in March 1934 and the last in March 1936. Our observations cover a maximum period of three years and nine months and a minimum period of one year and nine months. Five additional patients have been operated on since March 1936, 3 of whom at the time of writing have remained completely well for one year and 2 of whom remain improved after a shorter period. However, it is felt that the period of observation in their cases is not long enough to permit the drawing of definite conclusions. No deaths which could be attributed to the operative procedure have occurred.

OPERATIVE TECHNIC

The patient is placed on the operating table in the semiprone position, and the side to be operated on is elevated by means of a sand bag placed beneath the anterior thoracic region. The arm is allowed to fall to the side and is loosely fixed at the table edge. After the skin has been prepared by careful cleansing with ether, a 3.5 per cent solution of iodine

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Lehre vom Asthma, Ztschr. f. klin. Med. **5**:413, 1882. Einthoven, W.: Ueber die Wirkung der Bronchialmuskeln, nach einer neuen Methode untersucht, und über Asthma nervosum, Arch. f. d. ges. Physiol. **51**:367, 1891. Beer, T.: Ueber den Einfluss der peripherem Vagusreizung auf die Lunge, Arch. f. Physiol., 1892, supp., p. 101. Dixon, W. E., and Brodie, T. G.: Contributions to the Physiology of the Lungs: I. The Bronchial Muscles, J. Physiol. **29**:97, 1903. Weber, E.: Neue Untersuchungen über experimentelle Asthma und über die Innervation der Bronchialmuskeln, Arch. f. Physiol., 1914, p. 63.

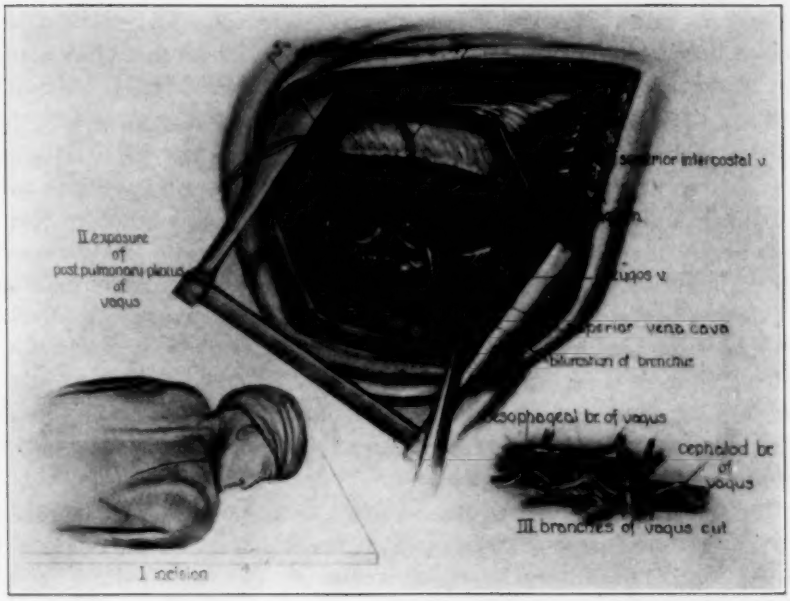

Fig. 1.—Resection of the posterior pulmonary plexus on the right side, showing incision and exposure of the posterior aspect of the hilus of the right lung.

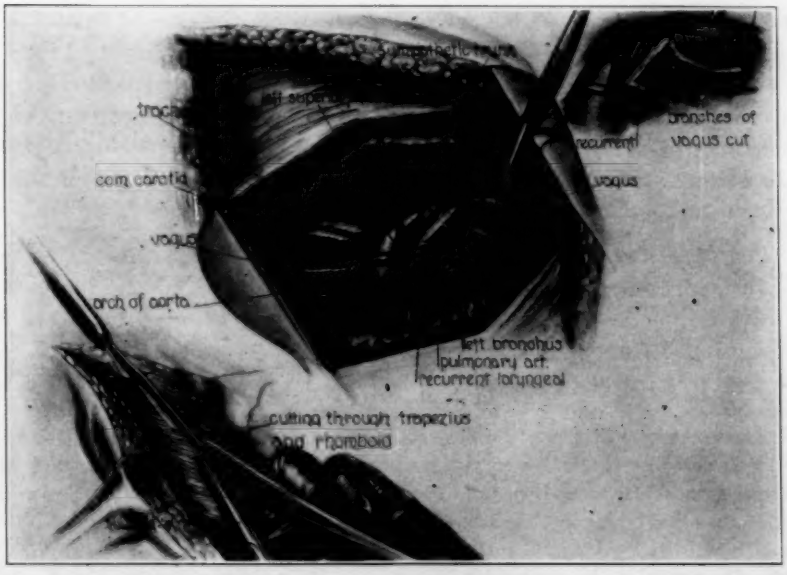

Fig. 2.—Resection of the posterior pulmonary plexus on the left side. The incision is carried down through the skin into muscle. Note the exposure of the vagus nerve and the posterior aspect of the hilus of the left lung.

is applied. This is removed with alcohol; the operative field is isolated in the usual manner by proper draping, and an incision is made in the interscapular region. The incision is begun on a level with the spinous process of the first thoracic vertebra, about 8 cm. below the upper border of the trapezius muscle and approximately 6 cm. lateral to the midline. It is continued downward and somewhat laterally to just below the angle of the scapula. The concavity of the incision faces lateralward and is in a general way parallel to the vertebral border of the scapula. The incision is similar to that used in the operation of posterior thoracoplasty but is not quite as long. The skin and subcutaneous tissue having been divided, the fascia covering the trapezius muscle is incised, and the fibers of the latter are divided directly over the fourth interspace on the right side and over the fifth on the left. In a similar manner the fibers of the rhomboid major muscle are also cut across. The incision is then continued down through the intercostal muscles, midway between the corresponding ribs so as to avoid the intercostal vessels and nerve. The pleural cavity is opened, and a self-retaining retractor is placed between the ribs in order to separate these sufficiently to expose the posterior surface of the hilus of the lung. As a rule, an intercostal incision of approximately 12 cm. will give sufficient exposure. It is true that the ribs are more closely approximated posteriorly, but even so they may be sufficiently separated. If not, one rib may be divided by means of rib shears. It has not been found necessary to resect a rib. In only a small percentage of cases have adhesions between the visceral and the parietal pleura been present, and such adhesions have always been easily dissected apart. Once the pleural cavity is opened, the posterior surface of the primary bronchi is exposed. A slight anatomic difference exists on the two sides. On the right side it has been found helpful to locate primarily the azygos vein, immediately inferior to which may be found the right primary bronchus. The vagus nerve is then discovered by incising the mediastinal pleura just cephalad to the azygos vein. It is important to locate the nerve at this point, for either just above or at the same level as the vein (or not infrequently even directly posterior) a rather large branch departs from the vagus and runs along the upper posterior border of the right pulmonary artery. The right vagus is then further exposed and mobilized from above the azygos vein in the posterior part of the mediastinum to a point below that at which the branches to the esophageal plexus depart. This point is well below or caudal to the hilus of the lung, but these branches to the esophageal plexus should be divided. The fibers running from the vagus and sympathetic trunks to the homolateral lung and the contralateral lung are thus readily and easily exposed, so that resection of at least 1 cm. of each of the nerve fibers may be accomplished. It is of the utmost importance to sever all of the branches of the posterior

pulmonary plexus not only to the same side but to the opposite side, for, as will be pointed out, this plexus contains the bronchoconstrictor fibers of both the vagus and the sympathetic trunk. The main trunk of the vagus should be handled as delicately as possible, so as to produce the minimum amount of trauma and therefore the least interference with function. For the sake of thoroughness it has become our custom to remove all areolar tissue from and around the bronchi and vessels in order to divide any unnoticed fibers which might course directly to or from the sympathetic trunk. In this manner the lung may be completely denervated. By elevation of the intratracheal pressure to 15 mm. of mercury the lung may be reexpanded and the air forced out of the pleural cavity. The ribs are then reapproximated with pericostal sutures of braided silk, and the muscles and fascia are sutured with interrupted stitches of fine silk. The skin is closed with interrupted fine silk sutures.

After two weeks the procedure is repeated on the left side, the only difference being that better exposure of the posterior surface of the hilus may be obtained by placing the intercostal incision one interspace lower on the left side, that is, in the fifth interspace. The vagus trunk will be found coursing over the transverse arch of the thoracic aorta, and the departure of the left recurrent or inferior laryngeal nerve may be observed just under the arch. The main trunk of the left vagus from this point down to that at which the first branch to the esophageal plexus is given off should then be freely mobilized and the fibers entering into the formation of the posterior pulmonary plexus exposed. As has been stated, resection rather than simple division of this plexus must be carried out, not only on the fibers running to the same side but also on those running to the contralateral side. The inferior or recurrent laryngeal nerve should be carefully avoided, for handling or even slight traction on this branch will produce temporary paralysis of the left vocal cord, resulting not only in transient aphonia but in some difficulties of breathing and deglutition. Such a complication produces an unfavorable psychic effect on the patient. In other respects the operative technic for the two sides is identical. The operation may be performed in a short time with no loss of blood, and in our series of cases it has been unattended by shock. There have been no postoperative complications after the procedure. The anesthetic employed has been either nitrous oxide and oxygen or cyclopropane, and a tight-fitting mask rather than an intratracheal tube has been used. Two-tenths gram of sodium amytal or pentobarbital sodium has been administered by mouth on the night and early morning preceding the operation. There have been no respiratory complications. In 3 cases after primary denervation of the left lung the right vagus trunk was divided deep in the neck, just below the point at which the recurrent laryngeal nerve is given off. After this procedure there was abdominal distention, lasting from forty-eight to

ninety-six hours, which was attributed to interference with the left vagus trunk as a result of handling. There was also, of course, complete loss of function of the right vagus caused by section. This type of procedure on the right side is not comparable to resection of the posterior pulmonary plexus from the standpoint of thorough denervation of the lung, because bronchoconstrictor fibers from the right vagus are given off high in the neck and course down the right sympathetic trunk; in the region of the second and third thoracic sympathetic ganglions they leave this trunk and join the posterior pulmonary plexus. With our patients, although there has been marked improvement as to both the frequency and the severity of the asthmatic attacks, there has been some persistence of mild and infrequent attacks. In the near future complete denervation of the right lung will be performed in such cases with the hope of completely eliminating the attacks. Procedures falling short of complete denervation of the lung by bilateral resection of the posterior pulmonary plexus are inadequate.

POSTOPERATIVE COURSE

Generally speaking, in all cases in which bilateral resection of the posterior pulmonary plexus has been performed the postoperative convalescence has been uneventful. The following exception should be noted: One patient, an elderly Negro, died several weeks after the second stage had been completed. The patient had suffered for years from asthmatic seizures associated with a high degree of arteriosclerosis, hypertension and some chronic myocardial change. He died suddenly after a cerebral hemorrhage unassociated in any way with the operation and after his asthmatic attacks had disappeared completely. Nothing abnormal was discovered in the heart, the lungs or the pleural cavity at autopsy. For the remaining patients the postoperative course was remarkably uniform, almost stereotyped. After the effects of the anesthetic had worn off following the completion of the first stage, the patient still had attacks of asthma. These attacks occurred almost as frequently as before but were far less severe, and much less epinephrine was required to bring about a subsidence of the seizure. One $\frac{1}{100}$ grain (0.6 mg.) of atropine would always bring about amelioration of an attack after the completion of the first stage of the operation. This has been considered of definite significance because of the well known paralyzing effect of atropine on the vagus nerve. In a larger series of cases the beneficial preoperative effects of atropine may furnish data that will prove helpful in selecting for operation only those patients with whom the condition is primarily neurogenic. On physical examination after the completion of the first stage it was discovered that most of the signs of bronchoconstriction were confined to the side of the chest on which no operation had been performed, and that probably

the sibilant, piping and squeaking rales audible on the surgically treated side were transmitted. A partial pneumothorax as a contributing factor in the production of these phenomena was excluded by a roentgenogram of the chest. During these unilateral asthmatic attacks the production of sputum was definitely reduced. No disturbance of respiration, either in rate or in rhythm, could be observed. After the second operation the frequency of the asthmatic attacks was generally much less, and there was an even more pronounced reduction in the severity of the attacks and their duration. In some patients the attacks ceased entirely. In the early weeks of reconvalescence the amount of sputum expelled was scanty compared to the copious amount produced before operation. One of the most striking results of the denervation was the disappearance of emphysema, which was present preoperatively in all cases. This was determined primarily by auscultatory findings and also by roentgenograms. The depth of respiration was greater after operation, while the rate decreased. In other words, the patients' respiratory mechanism more nearly approximated the normal. Unquestionably a great deal of the inspiratory and expiratory stridor caused by spasm of the bronchoconstrictor muscles as well as by excessive secretion of the bronchial glands could be explained on the basis of previous overactivity of the vagus nerve. Likewise, interference with the function of the vagi would relieve the patient of these difficulties provided such an aberrance of function were the underlying cause. This sequence of events, therefore, would seem to suggest that in the type of case dealt with in this series overactivity of the autonomic nervous system and particularly of the vagi played the major role in producing the attacks of paroxysmal respiratory dyspnea termed asthma. That there may have been some other factor or factors, such as infection or allergy, which furnished the immediate cause of the attack cannot be gainsaid in our present state of knowledge, but that removal of the influence of the extrinsic nerves was greatly beneficial in the majority of our cases and curative in some cannot be denied.

LATE RESULTS

A continuous follow-up study of these cases has been carried out, and for certain patients the postoperative convalescence as well as the subsequent clinical course has varied to some extent. These variations are noted here to emphasize the complexity and multiplicity of the factors producing such paroxysmal attacks of respiratory distress and to suggest that although the original causative factor has been removed, nevertheless in some cases in which the condition is of long standing the pathologic sequelae of these attacks may of themselves produce paroxysmal respiratory disturbances similar to the original asthmatic injuries.

Of the 10 patients discharged from the hospital, 1 was entirely unimproved; 1 improved for three months, finally succumbing to what seemed to be cardiac failure (this case will be discussed at greater length); 4 are completely well at the time of writing, having been free of attacks since operation or a short time later, and are able to resume their former work; 4 have occasional mild attacks of asthma, all of which are amenable to control by means of small doses of ephedrine.

The patient in whose condition there was no improvement after the operation was a poorly nourished Negro aged 56. He had chronic syphilis. He had been given antisyphilitic treatment for some time, but in spite of this aortitis had developed, resulting in insufficiency of the aortic valves. Whether or not this condition had any bearing on the continuation of his attacks of respiratory difficulty after operation is debatable, but it is at least within the realm of possibility that attacks of bronchial asthma superimposed on preexisting damage to the heart might have such a deleterious effect on the cardiac mechanism and consequently on the pulmonary circulation as to cause attacks of paroxysmal dyspnea almost indistinguishable from true bronchial asthma. However, the result in this case must be considered complete failure.

The second patient in whose case therapy failed was an engineer, referred to us by Dr. M. B. Cohen of Cleveland. The patient had been completely incapacitated before operation. His preoperative condition was almost one of status asthmaticus; he was confined, of course, to his bed and was forced to remain in the sitting posture practically the entire twenty-four hours. He had been studied most carefully in several clinics, and the condition was found to be unamenable to all forms of medicinal therapy. In spite of large doses of epinephrine administered daily for a number of years, the clinical course of his asthma had been continuously more severe. A copious amount of sputum was coughed up in the twenty-four hours, and there was pronounced emphysema. The patient was operated on, the posterior pulmonary plexus of one side being resected. After this procedure the asthmatic attacks were greatly reduced in severity as well as in frequency, and the amount of sputum was definitely diminished. For the first time the patient could sleep in the recumbent posture, and breathing was without effort. One afternoon the patient was asleep, breathing easily and normally. He was awakened by one of us, who talked on general subjects for some time. There was no disturbance in the respirations of the patient until he was informed that operation would be performed on the other side the next morning. In less than five minutes he was seized with a severe attack of asthma. After completion of the second stage of the operation, the patient was much improved for three months, during which time he was up and about and was considering a return to work. The sputum was reduced in amount, and the emphysema disappeared almost entirely. However, after three months paroxysmal attacks of respiratory distress recurred and the patient succumbed some months later to what appeared to be cardiac failure.

The interesting points to be noted in this case would seem to be: (1) the psychogenic factor in production of an attack, observed between the first and the second operation; (2) the prompt and pronounced reduction in the amount of sputum and the striking disappearance of the emphysema, suggesting that overactivity of the vagi played a major

role in the production of these respiratory attacks; and (3) relief from the asthmatic attacks for a period of three months, followed by eventual death from myocardial insufficiency, suggesting at least the possibility that the terminal attack of respiratory difficulty might have been partly or even entirely due to congestive cardiac failure. Thus a terminal pathologic condition probably produced by asthmatic attacks arising from another and specific cause might in itself be responsible for a continuation of these clinically similar seizures. It is not at all impossible that in a patient who is afflicted with a reactive or labile psychic and autonomic nervous system secondary pathologic changes can be indirectly produced, which may eventually prove fatal. Frequent examples of this may be cited: Raynaud's disease; instances of fatal angina pectoris; so-called neurogenic bronchial asthma; and anaphylactic shock. Smooth muscle spasm, as noted in an entire finger which is blanched from angiospasm as in Raynaud's disease, would have a different effect if the left coronary artery were involved or if the smooth bronchial musculature were affected.

Of the 4 patients who are completely well at the time of writing, only 2 were relieved at once after the operation on the second side. The remaining 2 were much improved immediately after the surgical resection of the posterior pulmonary plexus, but several months intervened before complete disappearance of the attacks. With the remaining 4, whose condition is vastly improved but who cannot be classified as completely well, this delayed or gradual disappearance of the asthmatic seizures may be taking place, and eventually they may entirely recover from the attacks.

COMMENT

The rationale of the operative resection of the posterior pulmonary plexus is based on the fact that the extrinsic nerve supply of the lungs consists of two entirely independent tracts, which have been demonstrated by dissection.[2] These tracts on account of their anatomic location and course have been termed the vagus, or bulbar motor lung, tract and the sympathetic, or spinal motor lung, tract, respectively. The preganglionic bulbar bronchomotor fibers arise in the dorsal vagus nucleus. From this point of origin they run in the vagus nerve trunk without interruption through the cervical and thoracic portions until they reach the region of the hilus of the lung. At this point they depart from the main trunk of the vagus by numerous small branches, mainly to the same but also to the opposite side or lung. Thus these branches form a part of the posterior pulmonary plexus on either side and end in the ganglions situated along the posterior surface of the main or

2. Møllgaard, H.: Studien über das respiratorische Nervensystem bei den Wirbeltieren, Skandinav. Arch. f. Physiol. **26**:315, 1912.

primary bronchi. From these ganglions the postganglionic fibers are distributed through the lung to the bronchial musculature. In addition, the vagus nerve forms anastomoses with that of the opposite side not only in the cervical region but also directly beneath the root of the lung, as well as in the esophageal plexus. Once the fibers from the parent trunk have entered that of the opposite side, the greater number of them pass upward and are distributed to the lung of the corresponding side and that of the opposite side. Chiefly, the fibers between the vagi pass over in the first anastomosis.

According to all physiologic observations, the vagus in the human lung carries or contains mainly bronchoconstrictor nerve fibers. In certain animals, particularly the cat, the vagus carries bronchodilator as well as bronchoconstrictor fibers, but even in this animal the latter predominate. Stimulation of the distal end of the cut vagus in man and in animals produces bronchoconstriction of the same side and to a less extent of the opposite side. In addition to the anatomic proof, therefore, there is physiologic evidence of the crossed or bilateral innervation of the lungs through the vagi.

As shown by Iwama [3] in experiments on the cat, the vagus nerve gives off in the cervical region anastomosing fibers to the sympathetic trunk of the same and the contralateral side. In the trunk these fibers course superiorly as well as inferiorly, so that both the right and the left sympathetic trunk in the neck and chest contain nerve fibers from the right as well as the left vagus nerve trunk. In the same manner sympathetic nerve fibers from the cervical sympathetic trunks of the same and the contralateral side are distributed to the vagi. Thus the vagus and sympathetic nerve trunks are composed of not only sympathetic but also parasympathetic nerve fibers.

The peripheral dissemination of the spinal fibers which run in the sympathetic trunk is not clearly known. In fact, there is no morphologic evidence of a spinal bronchomotor tract, but the results of physiologic experiments make it impossible to doubt the existence of such a tract. From the foregoing description of the frequent anastomoses between the vagus and the sympathetic trunk in both their cervical and their thoracic portions it is at once evident that not only in man but in animals used for experimental purposes, that is, the dog and the cat, there exists a vagosympathetic trunk; therefore, the possibility of the error of stimulating the parasympathetic trunk is evident. Although to a less extent compared to the vagi, the sympathetic fibers make a

3. Iwama, Y.: Untersuchung über die periphere Bahn des Nervus vagus: I. Die markhaltigen Fasern des rechtsen Vagus, Folia anat. japon. **3**:215, 1925; II. Ueber den gegenseitigen Austausch der markhaltigen Nervernfasern der beiderseitigen Vagi am Brustteil, ibid. **3**:281, 1925; III. Die markhaltigen Fasern des linken Vagus, ibid. **6**:129, 1928.

definite contribution to the formation of the posterior pulmonary plexus. Unquestionably, afferent as well as efferent fibers are contained in these nerves running between the sympathetic trunks and the posterior pulmonary plexuses. There are probably sensory fibers accompanying the bronchomotor fibers in the vagus nerve also, but just as the bronchoconstrictor fibers predominate in the vagus, it seems likely that the sensory and bronchodilator fibers course mainly in the sympathetic trunk. The cells of origin of the vagus sensory tract, as is well known, lie in the ganglion nodosum, to which run fibers from the trachea and the lungs. Stimulation of the central trunk of the cut vagus or the intact vagus incites reflex narrowing or constriction of the bronchi.

Møllgaard [2] has shown that in the second and third thoracic spinal sympathetic ganglions lie cells which apparently send off sensory fibers to the lungs. Central stimulation of the superior cardiac nerve, the ansa of Vieussens or the superior thoracic nerve also produces bronchial constriction.

From these anatomic as well as physiologic observations, it seems logical to state that there is a dual nerve supply to each lung, the anatomic course of which is through the vagus and also through the sympathetic trunks. The preponderance of the fibers is to be found in the vagi, which undoubtedly supply mainly the bronchoconstrictor fibers to the lung of the same side and that of the opposite side. Owing to frequent anastomoses with the sympathetic trunks, it seems likely that these carry similar fibers. The presence of bronchodilator fibers in the human being has not been proved, but if they are present they would seem to be much overshadowed by the constrictor fibers. The theory that the action of the sympathetic and that of the vagal fibers are antagonistic is also without foundation. That both trunks carry sensory fibers has been definitely shown, and that the majority run in the vagus trunk would seem to be firmly established.

Dysfunction or imbalance of this autonomic nervous system, although poorly understood, is now generally recognized as a generic term which covers a multitude of clinical manifestations, depending entirely on the organ or organs innervated by the two extrinsic nervous systems. It would seem that this disturbance of the normally evenly balanced action of the sympathetic and parasympathetic systems may be localized to one or more organs and may or may not affect the entire body. There is an abundance of clinical evidence to support this statement, that is (1) Raynaud's disease, in which the arterioles of the hands and feet are chiefly affected; (2) the various forms of functional cardiac arhythmia, such as paroxysmal tachycardia and premature systoles; (3) a small group of cases of essential hypertension; (4) ? diffuse goiter with severe hyperthyroidism, or exophthalmic goiter; (5) probably

some forms of migraine and minor cephalalgia, (6) many disturbances of the gastrointestinal tract, varying from cardiospasm, pylorospasm and spastic colon to Hirschsprung's disease; and (7) local dysfunction of the ureters and the bladder. All of these are but a few examples of pathologic disturbances which are either transient or prolonged evidence of an embarrassment or inequality of the normally symphonious action of these two antagonistic components of the vegetative nervous system. The lungs or the upper portion of the respiratory tract may be the site of this form of disturbed innervation. The clinical signs and symptoms evolved depend, of course, on the function of the organ or tissues so innervated and on the type of patient afflicted. As a rule, the psychobiologic reaction of the patient is far more labile than normal. There is, therefore, a psychogenic factor to be dealt with in all such cases of imbalance of the autonomic nervous system.

There are, as every experienced clinician is well aware, many cases of coryza, rhinorrhea, sneezing, nocturnal choking spells, globus hystericus, atypical hay fever, various forms of hyperpnea, even dyspnea and finally attacks of so-called nervous or neurogenic asthma in which the pathologic condition is unquestionably due to functional disturbances of the autonomic nerve supply to a part or the whole of the respiratory tract and is not based on, but may be associated with, an allergic reaction or infection. It was to patients suffering from almost continuous attacks of asthma or status asthmaticus and totally incapacitated as a result of this malady that our attention was directed. After a long period of study and treatment in the asthma clinic of the Johns Hopkins Hospital, this condition has been given up as hopeless from the standpoint of medicinal therapy and referred for surgical treatment as a last resort. It is felt desirable to report this actually small but relatively large group of cases at this time because about four years has now elapsed since the first operation was performed. Unquestionably there are many causes of bronchial asthma, and, as would be expected, the literature on this subject is voluminous. One of the most outstanding monographs is that of Alexander, which affords a detailed discussion of the causes and effects of this malady. It seems likely that the mechanism involved in the production of an asthmatic attack is unquestionably a narrowing of the bronchial tube with a subsequent increase in the resistance to the free inflow and outflow of air. This state of stagnation of ventilation indirectly produces changes in the blood gases and results in dyspnea of a greater or lesser degree, depending on the extent of occlusion of the bronchial tree. This occlusion may be considered as largely and in its simplest terms due to: first, spasm of the bronchoconstriction muscles; second, edematous swelling of the mucous membranes of the smaller bronchioles; third, increase in the amount and viscidity of the

secretion of the bronchial glands. In all instances of bronchial asthmatic attacks the three aforementioned factors probably play a major role, in spite of the additional etiologic factor or factors which may be involved in the production of such attacks. In many cases the asthmatic attacks can be explained directly on an allergic basis or indirectly on an infectious one. In some, however, when the former two causes have been eliminated the attacks can be ascribed only to a disturbance in the function of the autonomic or extrinsic nerve supply to the lung. The resultant effect on the bronchoconstrictor muscles, as well as the increased activity of the mucous membrane with its concomitant edema, and also the altered character and increased amount of the bronchial secretion produce a narrowing of the airways, causing associated dyspnea and other physical symptoms. The mechanism of production of an asthmatic seizure may be at least markedly influenced by the extrinsic nerve supply to the lung.

Doubtless in the majority of cases an important psychogenic factor is associated with a definite imbalance in the extrinsic nerve supply to the lungs. Along with this rather labile psychoneurogenic mechanism there may or may not be present a concomitant allergic or infectious element that plays a role of greater or less importance in the precipitation of attacks of asthma. In all probability such attacks of paroxysmal dyspnea associated with generalized bronchoconstriction and bronchorrhea and called asthmatic attacks are caused by many different etiologic factors. In some the psychoneurogenic element predominates, while in others infection or allergy plays the major role. In all, however, there is a large nervous element. The discovery of an allergic basis for attacks of bronchial asthma and their relief by medicinal measures form one of the most brilliant advances in therapeutic knowledge in the last few decades. However, although large, the group of patients with allergic asthma is far from all-inclusive, excluding as it were all of those persons in whom the psychoneurogenic or infectious element or both might be considered causative. Unfortunately for the latter patients, numerous different forms of therapeutic measures have been resorted to, and in spite of medicinal treatment the attacks continue unabated.

After medicinal methods had been exhausted in a futile attempt to alleviate the attacks for this most unfortunate group of patients, other forms of therapy were resorted to, such as high voltage roentgen therapy, injection of alcohol into the sympathetic trunk on one side and numerous operative procedures. For an excellent review of the many and bizarre operations which have been devised, performed and evaluated from the postoperative results, the splendid article by Phillips and

Scott [4] should be referred to. The failure of surgical treatment in the majority of cases of bronchial asthma in the past as well as the mediocre results obtained in the remainder, or minority, of cases may, it would appear, be attributed to the fact that the operations have been entirely inadequate. In some only the sympathetic trunk on one side has been severed; in others only one vagus trunk has been severed; in a very few a unilateral excision of the posterior pulmonary plexus has been performed. The course of the fibers composing the posterior pulmonary plexus makes it mandatory to perform a meticulous bilateral resection of the latter in order to isolate the lung completely from its extrinsic nerve supply. Any procedure short of this will be inadequate. It necessarily follows that the postoperative results will correspond directly to the degree of completeness with which the operation is carried out. The posterior aspect of the hilus is the only point at which all the efferent and afferent fibers composing the extrinsic nerve supply to the lung can be interrupted. It seems likely that because of this fact the operative results in the series of cases reported on here have been better than any of those reported in the past.

The ideal result, that is, complete cure, will of course be confined to cases in which the attacks of asthma are entirely psychoneurogenic and are not of many years' duration. An operation of this type can relieve only bronchoconstriction, edema of the mucosa and bronchorrhea which is vagal in origin. The greater the role played by allergy or infection, the greater the departure will be from this ideal result. On the other hand, even if a complete cure cannot be obtained, relief in varying degrees may be given. This not only will result in an infinitely more comfortable life for the patient and make it possible for him to return to work, but (a fact of greater importance) may remove the strain from an already overtaxed heart. When secondary pathologic changes have been wrought over a period of years and irreparable damage has been done to the heart muscle, attacks of paroxysmal dyspnea, cardiac in origin, may supervene even though the true asthmatic seizures have disappeared or have been very much subdued. When this occurs, the patient, as a rule, dies from circulatory failure of the pulmonary system, due in the main to myocardial weakness. For these reasons careful cardiovascular surveys should be made before a patient afflicted with paroxysmal attacks of dyspnea is subjected to an operative procedure of this type. On the other hand, a patient incapacitated from asthmatic attacks of unknown cause should be so operated on, not only because the operation may restore him to normal health but also because it may at least alleviate the attacks sufficiently to prevent further damage to the cardiovascular system.

4. Phillips, E. W., and Scott, W. J.: Surgical Treatment of Bronchial Asthma, Arch. Surg. **19**:1425 (Dec., pt. 2) 1929.

BEHAVIOR OF JOINT CARTILAGE IN LATE RICKETS

CONTRIBUTION TO THE QUESTION OF ATROPHY OF CARTILAGE

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Considerable work has been done to clarify the morphologic changes of the zones of enchondral growth in patients with rickets, and hardly anything new can be added. However, investigators doing such work have paid little attention to the behavior of joint cartilage, although one might think that a number of biologic questions concerning joint cartilage might be answered by such study. I mean, especially, the still debated question of the importance of enchondral ossification of joint cartilage for the growth of the epiphyses, and also the question whether simple atrophy of cartilage may occur. It is clear that simple rickets as it occurs in earliest childhood can hardly be of use for the study of joint cartilage, because the cartilage has not fully developed; the thick cartilage cap still completely surrounds the bony epiphysis. On the other hand, reports of careful anatomic examinations of patients with late rickets, in whom the joint cartilage is of more mature development, are rare; and even the best works on the subject, by Looser [1] and by Schmorl,[2] do not mention changes in the joint cartilages. I recently finished an article [3] on the roentgenologic and histologic changes observed in 3 cases of severe late rickets, and I have observed certain alterations in the joint cartilages which I consider worthy of separate mention.

I shall first give a short report on the 3 cases in which the condition was observed at autopsy during the World War, collected at the City Hospital of Vienna.

CASE 1.—A 15 year old girl had extreme deformities of all the extremities. The body length was only 87 cm. The patient had had rickets from childhood and had never walked. She had never attended school and was mentally retarded. She had scorbutic bloody suffusions of the lower extremities and gingivitis suppurativa with gangrene of the lower lip and the gum.

CASE 2.—A 22 year old woman of infantile habitus had gummatous osteoperiostitis of the skull and also syphilitic saddle nose. The body length was 142 cm.

From the Orthopedic Department, College of Medical Evangelists.

1. Looser, E.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **18**:678, 1908; Deutsche Ztschr. f. Chir. **152**:210, 1920.

2. Schmorl, G.: Deutsches Arch. f. klin. Med. **85**:174, 1905.

3. Freund, E.: On Three Cases of Late Rickets, Am. J. Roentgenol., to be published.

There were severe rachitic deformities of the spine and the extremities. Scurvy was present. The patient died of Spanish influenza.

CASE 3.—A 25 year old woman, an imbecile, underdeveloped and of infantile habitus, 126 cm. in body length, was supposedly normal until the age of 14. Late rickets was present; the patient could not sit or walk. Death was caused by pulmonary tuberculosis.

It is questionable whether one may expect to find specific rachitic changes in the joint cartilages. It is well known that the degree of alteration of cartilage in rickets depends on the inherent rapidity of enchondral ossification, which varies with different parts of the body. This explains the fact that a patient in whom considerable changes are observable at the costochondral junction may have no signs of rickets at a slowly growing epiphysial plate, for instance, the lower end of the humerus. It is well known, further, that rachitic changes appear only at the diaphysial side of the cartilage plate, which is the site of enchondral ossification, while the epiphysial side, owing to the inactivity of enchondral ossification, usually presents no rachitic signs. As far as enchondral ossification is concerned, the joint cartilage behaves similarly in many ways to the epiphysial side of the cartilage plate, which means that it presents little activity; and for this reason alone one must be prepared for failure to discover rachitic changes in the joint cartilage. However, it is logical to conclude that the enchondral ossification of joint cartilage represents the only possibility of enlargement of the bony portion of the epiphysis, and severe rickets, which leaves its marks on all the epiphysial plates of the body—and in most of the cases of late rickets observed during the war the condition was severe—will hardly leave the joint cartilage unaltered.

As a matter of fact, in the various joints which I examined I observed pictures which varied from the approximately normal, as in the elbow joints of the patient in case 1, to severe and unusual pathologic change, as in the knee joint of the patient in case 3. But even in the most severely affected joints the principal pathologic process could hardly be interpreted as rachitic; the changes were nonspecific and were due to atrophy. Even so, however, they were of considerable interest and were certainly related to the existing rachitic process.

The question has often been discussed whether joint cartilage, as a bradytrophic organ in which the number of cells once the cartilage has reached structural maturity remains more or less constant, can undergo atrophy, which means diminution of its cells, in the same way as other organs do.

SIMPLE ATROPHY OF JOINT CARTILAGE

Müller[4] in his book on the biology of the joints, stated that even in the most advanced forms of bony atrophy the joint carti-

4. Müller, W.: Biologie der Gelenke, Leipzig, Johann Ambrosius Barth, 1929.

lages do not show changes in the number of cells. I, however, feel that the discussion about atrophy of cartilage is much ado about a pseudo-problem. There is no doubt that joint cartilage can undergo atrophy just as does the underlying bone, and any one who has examined a number of senile joints will confirm this. Pommer's idea that bony atrophy in its simplest form results from a prevalence of physiologic absorption of bone over apposition of bone can also be applied to joint cartilage. Joint cartilage under physiologic use shows constant wearing off of cells and ground substance at its superficial layers. To compensate for the loss, the cartilage cells or cell groups in the deeper layers and at the margins of the joint cartilage proliferate. Under normal circumstances such proliferation is not a very active process, and it is hardly recognizable microscopically in adults. Its existence has been denied by some investigators because of lack of histologic evidence, and a form of amitotic division of the superficial cartilage cells has been assumed to compensate for the wear. Be this as it may, atrophy of joint cartilage must ensue as soon as the compensatory proliferation fails to keep pace with the wearing off of the upper layer. Such atrophy occurs in association with many forms of degenerative arthritis or in cases in which there is absorption of joint cartilage under a fibrous tissue pannus. In such cases thinning of the joint cartilage occurs by resorption or loss of cartilage from above, and the result is atrophy of joint cartilage.

ATROPHY FROM DISUSE

Another characteristic form of cartilage atrophy is that caused by disuse. Joint cartilage needs function for its preservation. It will slowly disappear when it is put out of action. Absorption takes place from the margins of the joint and from the bone marrow, and especially at the marginal portions of the joint surface which have lost normal contact with the antagonistic end of the joint, as in articular contracture. I recently reported [5] on the histologic changes of joint cartilage during infraphysiologic use and stressed their importance for the development of the final shape of the ends of the joint in cases in which disuse sets in at an early age. If disuse of a joint takes place in an adult, especially for extra-articular reasons, then the subchondral hard substances, the bony lamina and the calcified joint cartilage will disappear first, usually by osteoclastic absorption, and later a slow, smooth absorption of joint cartilage can be observed which may gradually lead to complete disappearance of the cartilage. Such pictures are not rare for paralyzed senile joints, with or without deformity and especially in the proximal fragment in case of nonunion of fracture of the neck of the femur. In

5. Freund, E.: Joint Cartilage Under Infra-Ultra and Euphysiologic Demands, Arch. Surg., to be published.

all such cases the atrophy of the joint cartilage corresponds to the bony atrophy of the joint ends; it is only a concomitant symptom of skeletal atrophy.

The 3 patients with adult rickets mentioned in this paper showed atrophy of articular cartilage in both forms; there was absorption from above by a fibrous tissue pannus, but the thinning out of joint cartilage was principally caused by smooth absorption from below. Signs of enchondral ossification of the joint cartilage, which might have been expected in all the joints because of the presence of epiphysial plates in other regions of the body, were rarely seen in the more severely involved joints. Cartilage proliferation especially, which was so pronounced at the epiphysial plates even in the patients aged 22 and 25, in whom it had caused tumor-like accumulation of cartilage cells, was entirely absent in the joint cartilage. It is certain that rickets does not stimulate cartilage proliferation; so even the tumor-like chondromatous masses at the metaphysial sides represent only accumulation of cartilage tissue which has formed during many years of retarded or absent enchondral ossification. It is not a sign of overproduction of cartilage, but only a sign of the persisting proliferative phase of enchondral ossification (which, as a whole, is probably considerably slower than normal, in accordance with the retarded growth and the general hypoplasia of the rachitic patient) and of the complete absence of the phase of ossification due to the lack of cartilage calcification. A noticeable accumulation of cartilage cells cannot be expected at the articular cartilage, the growth of which is physiologically very slow and in which absorption at the lower surface can easily keep pace with proliferation.

ENCHONDRAL OSSIFICATION OF JOINT CARTILAGE

One must also consider the fact that during normal epiphysial growth there is always a reduction of the thickness of the cartilaginous cap of the bony epiphysis. The reduction takes place by slow enchondral ossification, which leads to the enlargement of the bony epiphysis. It is a well balanced process of proliferation and ossification of cartilage, the latter being slightly predominant. When epiphysial growth stops, the cartilage cap has been reduced to the normal thickness of joint cartilage. This means that thinning out of the cartilaginous cover of the bony epiphysis which occurs by means of normal absorption is a somewhat more rapid process than proliferation. Both processes are slowed down in cases of late rickets; proliferation of joint cartilage is at a complete standstill, but absorption from the marrow spaces continues. The result must be that the epiphysis does not show any increase in size, though the bony portion may be enlarged very slightly at the expense of the joint cartilage. The lack of proliferation of the joint cartilage is another proof of the fact that rickets does not stimulate growth of cartilage.

PHYSIOLOGIC NECROSIS OF CARTILAGE CELLS

The most frequent histologic changes observed (fig. 1) were the following: The joint cartilage appeared rather thin but was mostly smooth on the surface. It usually permitted an easy differentiation into 3 layers. The most superficial one, comprising approximately two fifths of the thickness, could be considered as a gliding layer with fusiform cells parallel to the joint surface. A good many of these cells were only shadows, necrotic, in the stage of "Verdämmerung" (Schaffer [6]); they contributed by their transformation to ground substance to the enlargement of the intercellular areas. This was a sign that the joint

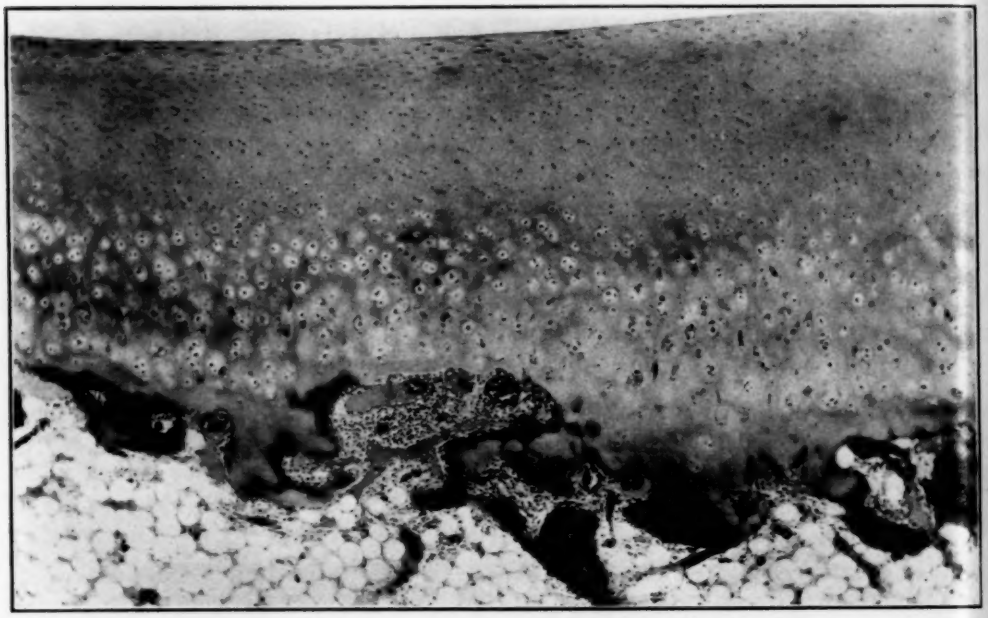

Fig. 1 (case 3).—Upper joint surface of the tibia, enlarged about 43 times, showing irregularity of the lower surface of the joint cartilage, which lacks a distinct zone of calcification and a subchondral bony lamina. There is a high degree of osteoporosis. Marrow spaces enter the noncalcified joint cartilage and replace it by fibrous tissue. The structure of the joint cartilage is immature. Enlargement of the cartilaginous cells has occurred in the lower half, with no increase of cellular proliferation. Note the infantile crisscross arrangement of cells in the upper half of the joint cartilage.

cartilage had not yet reached mature functional structure; in most joints it had remained in an infantile stage and the differentiation of its cells was deficient. The middle two fifths was characterized by relatively

6. Schaffer, J.: Lehrbuch der Histologie und Histogenese, ed. 3, Leipzig, Wilhelm Engelmann, 1933.

large cell cavities with proliferating cartilage cells, three to five in one cavity, with some clear bluish protoplasm which suggested the mucoid degeneration so frequently observed in older patients with degenerative cartilage proliferation. There were neither cell capsules nor pericellular halos; the hyaline ground substance lacked normal basophilia and bordered on the cell cavities without any tinctorial differences. It gave the impression of little consistency, which was suggestive of edema of the cartilage. The number of degenerating cells was greater in this region than in the superficial layers, and the relatively wide intercellular spaces permitted the discerning almost throughout of shadows of former cartilage cells. The edema of the middle layer of joint cartilage, which sometimes extended even into the superficial strata, made the cartilage appear of little mechanical resistance, which was contrary to a normal zone of passage between the superficial gliding layer and the deep pressure layer. The distribution of the cartilage cell groups was irregular; it was still more of the infantile crisscross arrangement and was far from being a functional structure with radial orientation of the cells, such as might have been expected from the relatively advanced age of the patients. The lowermost fifth was unusual. The cartilaginous ground substance in this region appeared darker and was evidently harder, and the cells formed small groups without proliferation and without elongation. This is remarkable because this deepest stratum of the pressure zone is usually during the years of skeletal growth the stratum showing the most active cellular proliferation. It is from this layer that replacement of the worn-off superficial cells takes place. Another surprising fact was that this layer was also the richest in necrotic cells. No special reason for this peculiar behavior could be discovered. It seemed, however, that although necrosis of cartilage cells and their transformation to hyaline ground substance are normal conditions in the period during which the joint cartilage acquires its mature functional structure, the number of necrotic cells in the joint cartilages studied was unusually high. It may be that nutritional deficiency accounted for it.

The manner in which the bone marrow bordered at the joint cartilage differed considerably from region to region. The patient in case 1, the youngest of the patients, showed a very irregular process of enchondral ossification with a deficient layer of calcification (fig. 2). Spots of calcified cartilage were sporadic and comprised only one layer of cartilage cells. There was no sharp line between the calcified and the uncalcified cartilage. Marrow spaces entered the cartilage with engorged vessels and ascended for a considerable distance into the noncalcified pressure layer (fig. 2). This was not according to a normal process of enchondral ossification; it rather resembled pictures of degenerative arthritis, of which Pommer considered the invasion of noncalcified cartilage by marrow spaces to be highly characteristic. In such cases it is the degenera-

tion of cartilage, especially the decrease in its elasticity, which fosters the invasion of marrow spaces as a reactive change from the side of bone marrow. It may be that similar alteration of the physical property of the articular cartilage takes place in cases of severe rickets, although the histologic evidence is relatively poor. However, the edema of hyaline ground substance and the frequent necrosis of cartilage cells suggest serious damage, to which the absorption by marrow spaces may be the direct response.

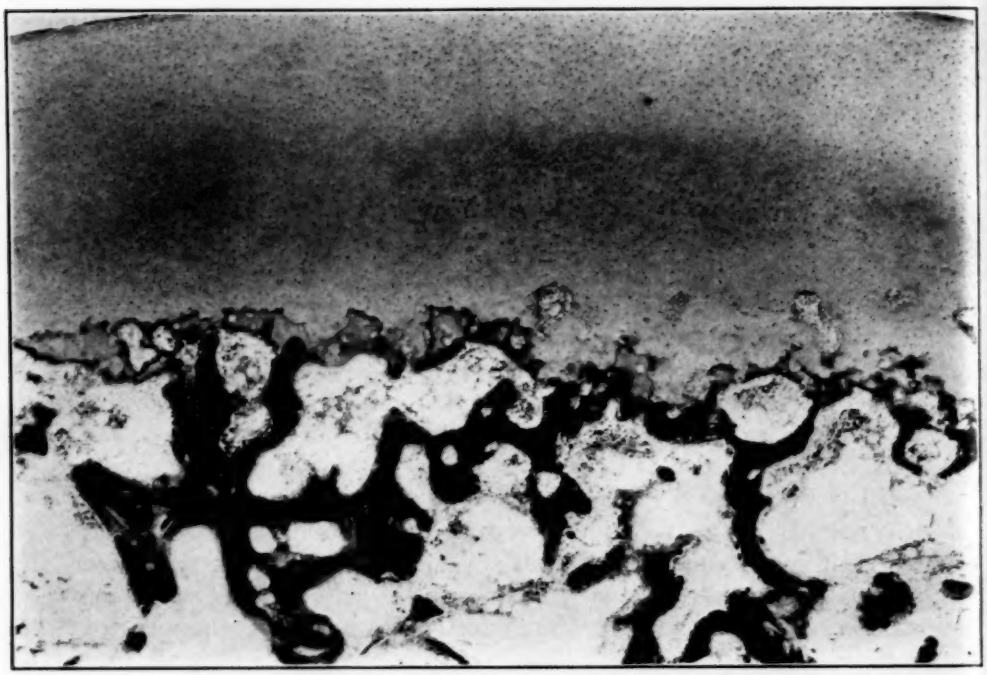

Fig. 2 (case 1).—Head of the femur of humerus, enlarged about 27 times. Note the typical rachitic changes in the subchondral zone and also the bony trabeculae, coarse and with wide osteoid layers. There is extensive osteoclastic bone absorption. The zone of calcification is irregular and is interrupted in many places by marrow spaces which deeply invade the noncalcified joint cartilage. The joint cartilage is without functional structure. There is beginning formation of intercellular territories in the lower half of the bone.

In these cases cartilage became absorbed by bone marrow along a fairly straight and sharp line more often than by small marrow spaces (figs. 3 and 8); it was a form of smooth absorption of the noncalcified cartilage after complete removal of the subchondral hard substances. Chondroclasts did not play an outstanding role in this form of absorp-

tion; they were rather rare, and the disappearance of cartilage, if it was a cellular process at all, was maintained by mononuclear fibrocytes. In both instances, whether there were smaller marrow spaces ascending far into the noncalcified cartilage or whether there were large marrow sinuses bordering directly on the lower surface of the cartilage, the result was the same; joint cartilage disappeared by a process of incomplete absorption and not by enchondral ossification. This means that the collagenous fibers of the cartilaginous ground substance persisted in part, and after their liberation from the hyaline cement substance helped

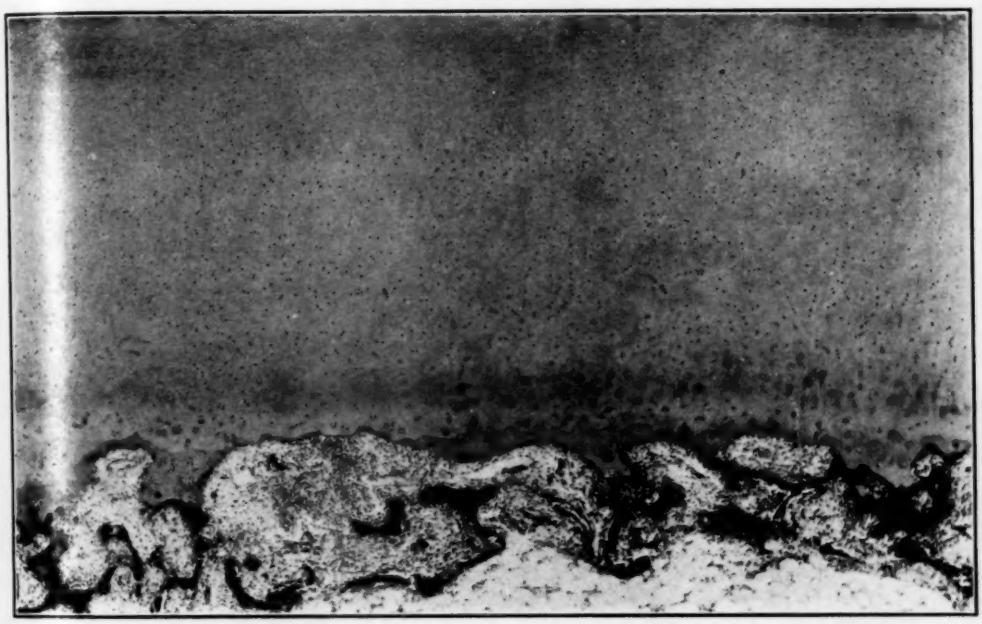

Fig. 3 (case 1).—Lower joint surface of the femur enlarged about 35 times. Note the smooth absorption of the joint cartilage from below and the formation of a subchondral zone of fibrous bone marrow and atrophic bony trabeculae. There is complete lack of a zone of calcification and of subchondral bony lamina. The structure of the articular cartilage is immature: there are no signs of cellular proliferation.

to form the subchondral bone marrow, which was typically loose fibrous tissue. It was possible in every instance to demonstrate how the fibrils of the bone marrow emerged directly into the hyaline ground substance, or, better, emerged from the cartilage and mingled with the fibers of the bone marrow. The joint cartilage disappeared without being replaced by bony tissue.

PERSISTENCE OF CARTILAGINOUS CELLS

The numerous marrow spaces along the lower surface of the joint cartilage often contained a number of isolated cartilage cells (fig. 4) or even smaller cell groups as they temporarily escaped the cartilage absorption. It seemed that the incomplete process of cartilage absorption often preserved not only the collagenous fibers which helped to form the subchondral fibrous bone marrow but also at least a part of the cartilage cells, which later, when the cell capsules had been dissolved, changed to fibrocytes and disappeared among the other cells of the bone marrow.

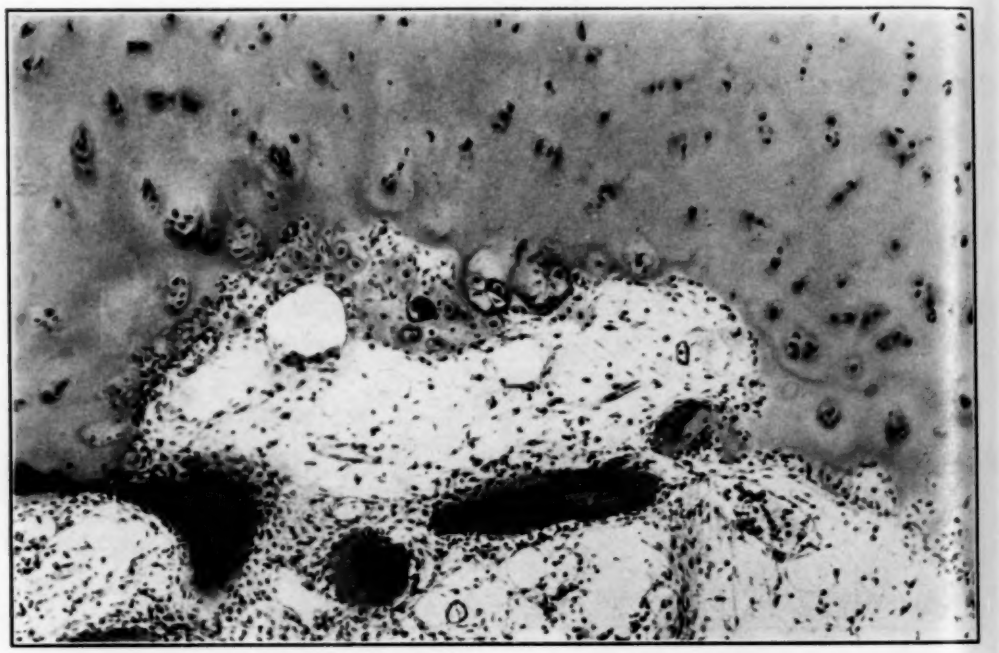

Fig. 4 (case 1).—Head of the femur, enlarged about 100 times. Note the incomplete absorption of the joint cartilage from below. Not also the loose fibrous bone marrow dissolving the hyaline intercellular ground substance. There is preservation of collagenous fibers and temporarily of cartilage cells and cell groups. The cartilage cells change to fibrocytes after the cell capsules have been dissolved. Note the wide osteoid layers of the bony trabeculae. Many cartilage cells in the stage of "*Verdämmerung*," merely shadows, add to the widening of the intercellular territories.

FILLINGS OF CARTILAGINOUS DEFECTS

Occasionally one noticed that some of the marrow spaces within the noncalcified cartilage had again become filled with a more primitive type of cartilage which certainly originated from the isolated cartilage cells (fig. 5). Such secondary "fillings" of marrow spaces are not unusual

in rib cartilages or in the hyaline cartilaginous plates of the intervertebral disk; they are also found in epiphysial plates and represent a change which is hard to classify as degenerative or reparative. They are extremely unusual in joint cartilages and were also rare in these cases of late rickets. Wherever they were observed the free surface of the joint cartilage was covered by a fibrous tissue pannus under which joint cartilage was absorbed along a rather sharp lacunar line, but with preservation of collagenous fibers and also of cartilage cells, which under proliferation changed to fibrocytes; that is, another process of incomplete cartilage absorption was taking place on the upper surface

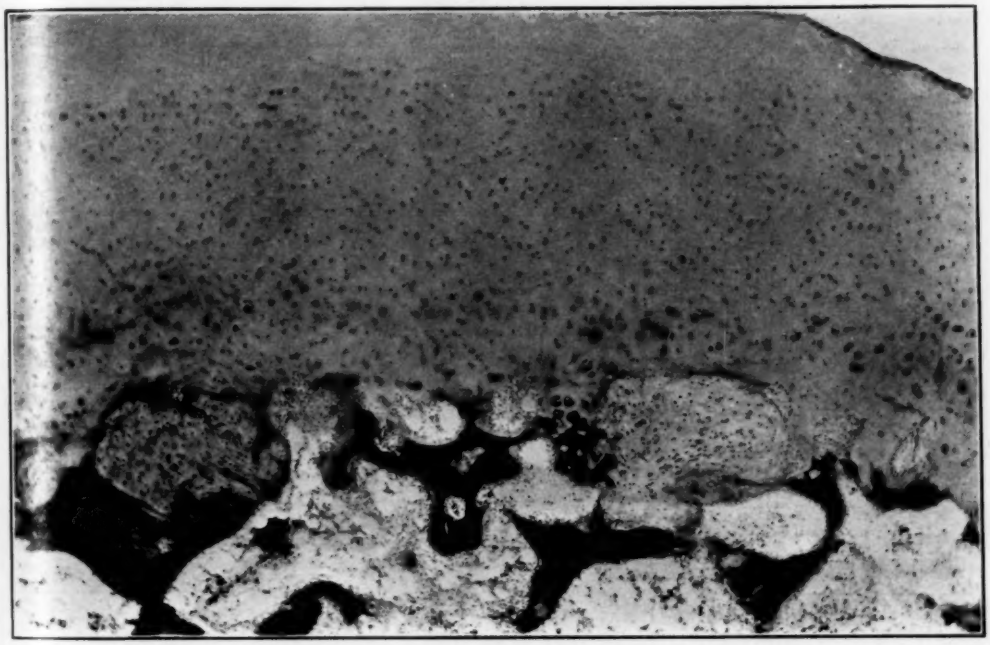

Fig. 5 (case 1).—Head of the femur, enlarged about 37 times. Note the filling of fibrous marrow spaces at the site of the joint cartilage by young proliferating cartilage tissue. Note also the typical rachitic changes of the subchondral bone and the primitive structure of the joint cartilage. There is beginning absorption of the superficial layers by an avascular fibrous tissue pannus. Most of the collagenous fibers derive from the hyaline cartilage itself, which by losing the hyaline chondromucoid cement substance exposes its collagenous fibers.

of the joint cartilage. The loss of cartilage on both surfaces, by a fibrous tissue pannus from above and by marrow spaces from below, suggests that the fillings of new cartilage at the lower surface represent a compensation for the thinning out of the joint cartilage from above. In all other places—and they are the majority—where there is only thinning from below, no attempt is made toward proliferation.

The loss of cartilage by absorption from below was one of the outstanding features in the behavior of joint cartilage in my 3 cases of late rickets. As a rule there was no cellular proliferation connected with this process. It had nothing to do with enchondral ossification; it was probably caused by an intrinsic physicochemical damage of the ground substance, by the inactivity of the joints, and as such it was a concomitant symptom of the severe atrophy of the skeleton. As has been mentioned, essentially the same type of atrophy of joint cartilage is frequently found in senile patients. For comparison I shall include an illustration of the broken head of a femur (fig. 6 and 7). The subchondral hard substances have disappeared almost entirely, and thickness

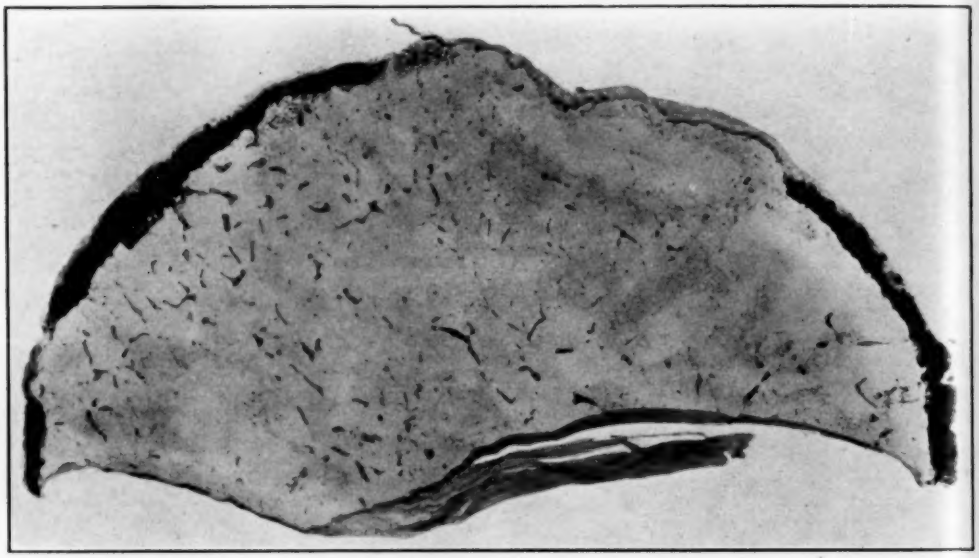

Fig. 6.—Broken head of the femur, without union, enlarged 3⅓ times. There is extreme bony atrophy with thinning of degenerated cartilage, mainly by smooth absorption from below.

of the joint cartilage has been reduced to about half or even less by resorption from below. Thus far the picture is identical with that described for late rickets. It is, however, surprising to note how much proliferative activity the senile joint cartilage displays, while in cases of late rickets there seems to be not the least effort to compensate for the loss. Of course, it cannot be denied that the proliferation associated with senile atrophy may be solely degenerative; if so, it should not be considered as an attempt at regeneration. It frequently occurs in senile patients with degenerative arthritis without atrophic changes in the subchondral zone. Whether it is called degenerative or regenerative proliferation, however, its effect is that joint cartilage invaded severely

by absorption from below will remain intact for a much longer period than it would without cellular proliferation, and one still wonders why the joint cartilage in cases of late rickets yields so readily to absorption. Changes in the physicochemical properties are present with senile atrophy of cartilage as well as with late rickets; the two conditions have inactivity and bony atrophy in common; and as far as regeneration is concerned, the patient with rickets should certainly possess more than the senile patient. Again one is driven to the assumption of a more specific damage of joint cartilage by rickets, a form of paralysis of the tissue caused by the nutritional disorder. (The apparent proliferation of cartilage at the epiphysial plates does not speak against this assumption, because, first, the different cartilage tissues of the body lead individual existences; one may be more active than another; and

Fig. 7.—Same section as in figure 6, enlarged about 27 times. The zones of cartilage calcification and the subchondral bony lamina have disappeared almost entirely. There is smooth absorption of the cartilage by bone marrow. There is proliferation of cartilage cell groups with erosion and fibrillation of the superficial cartilage layer.

also it is most unlikely that the tumor-like enlargement of the epiphysial plates is caused by superactive cartilage proliferation. It may be merely the expression of the lack of absorption of cartilage which has existed for several years.)

I feel, however, that there is still another factor which should be considered. There is no doubt that normal joint cartilage goes through a hard training during its many years of existence. This finds its morphologic expression in a highly mature functional structure which varies with the different types of joint. The high structural differentiation of the articular cartilages is usually taken as the main reason for the

lack of cartilage regeneration. Lubosch maintained that the high specificity of joint cartilage prevents further progressive development. This is certainly true, but the statement should not be taken as absolute proof that joint cartilage has not the power to regenerate. Mature hyaline cartilage is unable to produce cartilage tissue of like maturity to repair defects or injuries. All the regenerative phases are preceded by a backward development, in which the type of cartilage cells changes first to that of the fibrocytes, and then by further proliferation to a more primitive (fibrous) cartilaginous tissue. This inherent power to proliferate frequently can be observed in joint cartilage after all kinds of injuries. It may become manifest in senile patients when degenerative changes take place in the intercellular ground substance. It is a typical feature of degenerative and hypertrophic arthritis. It explains the considerable proliferation of the joint cartilage in the otherwise porotic fractured head of the femur.

The general underdevelopment of these 3 patients with late rickets and the fact that the joints of the lower extremities in cases 2 and 3 were hardly ever weight bearing suggest that the articular cartilages lacked special functional training and were not fit for survival. There was not enough vital force even for degenerative proliferation. The joint cartilages remained entirely passive and yielded to the absorption from below.

Occasionally a more or less coherent stretch of bony trabeculae, parallel to the lower surface of joint cartilage, indicated its former lower level. An extensive part of the joint cartilage had disappeared, either by smooth absorption without formation of fibrous bone marrow in the subchondral zone or because of the presence of small marrow spaces which later became confluent.

DISSECTION OF JOINT CARTILAGE BY ABSORPTION

The absorption of joint cartilage from below was not seen in every case to attack the deepest cartilage layer exclusively. Marrow spaces could be seen extending to the sides within the noncalcified pressure layer of the joint cartilage, thus separating a strip of cartilage as if by dissection. Such strips, often in connection with atrophic bone, sometimes persisted for some time, thus giving a landmark which showed how much of noncalcified cartilage had already become absorbed under extension of the intracartilaginous marrow spaces. This was again a picture similar to that observed with hypertrophic arthritis, with which exostoses develop at the site of the joint cartilage. In this condition also the deepest layers of joint cartilage, especially the calcified layer, may often persist in tonguelike form while the exostosis forms above them by enchondral ossification of the joint cartilage. The main difference

between the two processes consists in the fact that in late rickets the joint cartilage is entirely passive and there is almost no osteogenesis at its previous site, while in hypertrophic arthritis it proliferates, thus causing displacement of the joint surface to a higher level. (Or, because the joint cavity represents only a fictitious space which does not permit the enlargement of the joint end toward or into the joint cavity, the convex joint end is gradually displaced from the articulation [subluxated] to the extent to which the joint ends enlarge by enchondral ossification of the cartilage.) One might feel especially on the basis of Pommer's investigations and interpretations, that the absorption of joint cartilage by bone marrow is a sign of arthritis deformans. However, this would signify an overemphasis of the histologic picture. I do not share Pommer's conviction that the invasion of noncalcified joint cartilage by marrow spaces is of pathognomonic importance; it occurs too often as an entirely nonspecific response of bone marrow to essentially different lesions of joint cartilage. Rather than with arthritis deformans (hypertrophic arthritis) I should correlate the smooth absorption of the articular cartilage in my cases to atrophic changes; the numerous small marrow spaces doubtless resulted from incomplete cartilage absorption in atrophic arthritis. In such cases, in subacute and chronic stages there are typically rather vascularized marrow spaces in the lower layers of the joint cartilage; as a rule, however, bone formation at the former site of the joint cartilage does not ensue. This means that the similarity of the histologic pictures is merely external. In cases of atrophic arthritis and in my cases of rickets the joint cartilage is entirely passive and there is no enchondral ossification; simple substitution of cartilage by fibrous bone marrow takes place. With hypertrophic arthritis the joint cartilage proliferates and is replaced by bony tissue under enchondral ossification. There is rejuvenescence of articular cartilage in cases of hypertrophic arthritis, while in cases of atrophic arthritis and late rickets the cartilage is passive.

In some regions in which there was dissecting absorption of joint cartilage, two zones of preparatory calcification could be seen, defective it is true, corresponding to the associated hypocalcemia, but present nevertheless, and parallel to each other; one (the older) bordering directly on the subchondral marrow spaces and the other forming the upper border of the dissecting marrow space. One might think that one dealt in these cases with the manifestation of a remission in the rachitic process, which often leads to the parallel arrangement of cartilage calcification in the proliferated and widened epiphysial plates. Such an assumption, however, can easily be ruled out, because the strip of cartilage interposed between the two zones of calcification was free from cellular proliferation, that is, it did not represent a zone of cartilage proliferation, and the two zones of calcification belonged to two

different processes of enchondral ossification, which were entirely independent from each other (figs. 8 and 9). However, the fact that there was a zone of preparatory calcification makes one think that most of the resorptive changes at the lower surface of the joint cartilage, atypical as they were, nevertheless were somehow related to the physiologic enchondral ossification of the joint cartilage. They had become modified, often to such a degree that from a histologic standpoint they did not even suggest enchondral ossification.

There is still the question why there should be dissecting absorption of joint cartilage if there is no enchondral ossification. As a reason may be advanced the assumption that the absorbing marrow spaces could

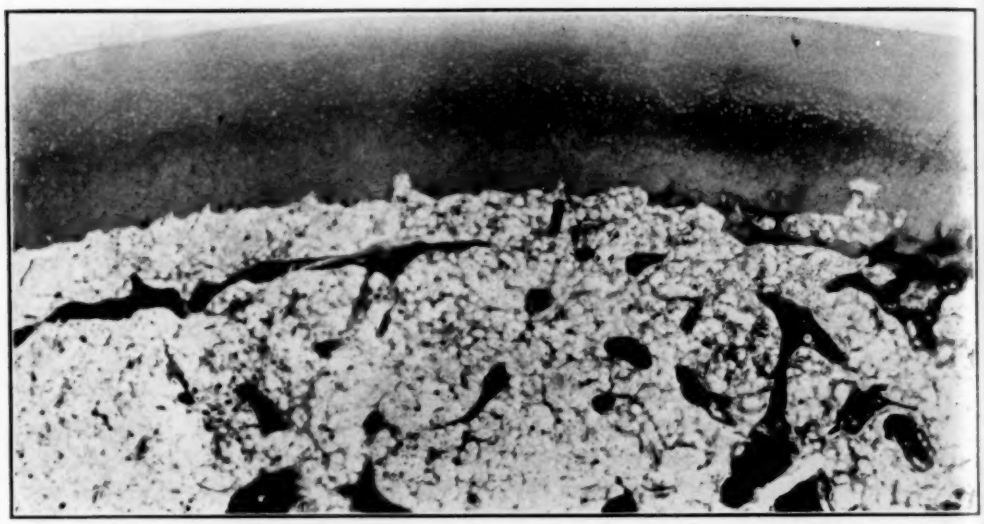

Fig. 8 (case 2).—Condyle of the femur, enlarged about 18 times. This photomicrograph is a good demonstration of loss of joint cartilage by smooth absorption from below. A series of bony trabeculae running parallel to the lower surface of the joint cartilage still indicates the level of the former subchondral hard substances. The cartilage yields by smooth absorption without formation of fibrous bone marrow. There is a marked degree of marantic atrophy of fatty bone marrow.

expand much more easily in the middle layer of the joint cartilage, where the intercellular ground substance is edematous and much softer and the cells showed more proliferation than in the deepest layer.

FIBROUS TISSUE PANNUS

Owing to the complete inactivity of the joints, the discovery of a fibrous tissue pannus extending from the joint margin over the free surface of the joint was nothing unusual, and some of the joints revealed

even partial obliteration of the joint space. A synovial pannus formed at the site of reflexion and firmly united the joint cartilages of both antagonists without visible alteration of the cartilage structure, producing fibrous ankylosis due to long-lasting inactivity.

DEFORMATION OF JOINT SURFACE

It is surprising that the extreme atrophy of the joint ends had not led in more frequent instances to deformation of the joint cartilage. There is no doubt that the undermined joint cartilage lacked solidity and could have been impressed easily by a relatively mild trauma. Only the

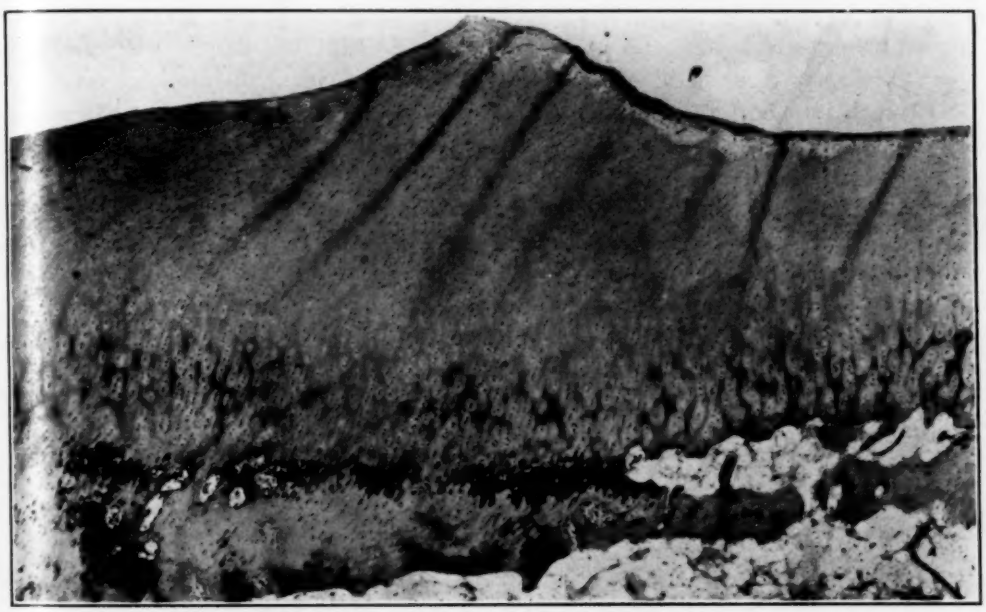

Fig. 9 (case 2).—Condyle of the femur, enlarged about 27 times. Note the dissecting absorption of the joint cartilage and also the enlargement of marrow spaces within the lower half of the joint cartilage. The expansion of the marrow spaces follows primitive and irregular calcification of joint cartilage at a higher level than the true zone of cartilage calcification could be expected. The dark streaks through the cartilage are artificial and are caused by the unevenness of the section. There is absorption of the joint cartilage from above by a fibrous tissue pannus.

lateral condyle of the femur in case 3 showed unevenness of the joint surface and an extensive callus formation of primitive fibrous osteoid in the subchondral zone. This suggested that a fracture had occurred through the extremely porotic bone, although there were no additional histologic signs of fractured bony trabeculae. This fracture had also

drawn the joint cartilage into participation. The cartilage at the joint margin showed irregular fold formation, which was partly active, owing to cartilage proliferation and elevation of the joint surface, and partly passive, owing to the extreme osteoporosis of the epiphysis and the mechanical displacement of the joint cartilage toward the bone marrow. The folded joint cartilage lacked normal structure. It had lost hyaline ground substance to a considerable degree, while the cartilage cells showed more active proliferation than was observed in any other part of the various joints. The picture changed thus by absorption of the hyaline cement substance from hyaline cartilage to fibrous cartilage and even to simple fibrous tissue. The proliferating cartilage cells reduced the intercellular septums of ground substance more and more to a rather regular network in the meshes of which lay the proliferated cartilage cells. The folded cartilage, despite its proliferation, was much thinned by smooth absorption from the bone marrow. Not fastened to the subchondral hard substances, the proliferating joint cartilage had a chance to expand to the sides as well as in height. (As long as joint cartilage is fixed by its calcified layer to the underlying bone, it can by proliferation increase only in thickness.) The increase in thickness was less noticeable because of the fact that there was constant and fairly active absorption from below. The expansion to the sides, however, led to the pleat formation as an adaptation to the disproportion between the size of the bony epiphysis and the enlarged cartilaginous cap. It is certainly remarkable that fold formation, such as I have seen in a number of different cases and even in the atrophic joints of senile persons, is such a rare observation in cases of late rickets. The almost complete inactivity of the joints, which keeps away the traumatic factor necessary for the passive form of fold formation on one side, and the lack of cartilage proliferation, which prevents the active form on the other, explain the rarity.

The surface of the folded cartilage was covered by a rather dense fibrous tissue pannus with synovial endothelium. It was especially thick over the valleys of the folds, in which the fibrous tissue was looser and contained a few capillary vessels. This somewhat smoothed the unevenness of the surface. The cells of the superficial cartilage layers under the pannus showed widening of the cell cavities and activity of the cartilage cells which changed to fibrocytes—Weichselbaum's lacunae. By confluence of several lacunae the joint cartilage changed to fibrous tissue. This was the third factor which led to thinning of joint cartilage.

INCOMPLETE ABSORPTION OF CARTILAGE

Another change of joint cartilage (fig. 10) should be mentioned. Almost the entire lower half of the thickness of the articular cartilage had lost the hyaline character; most of the cement substance had dis-

appeared, and the collagenous fiber bundles of the cartilage were clearly visible in almost straight perpendicular formations. Most of the cartilage cells freed from the surrounding cement substance had made a retrogressive change and appeared as fibroblasts, many only as shadows

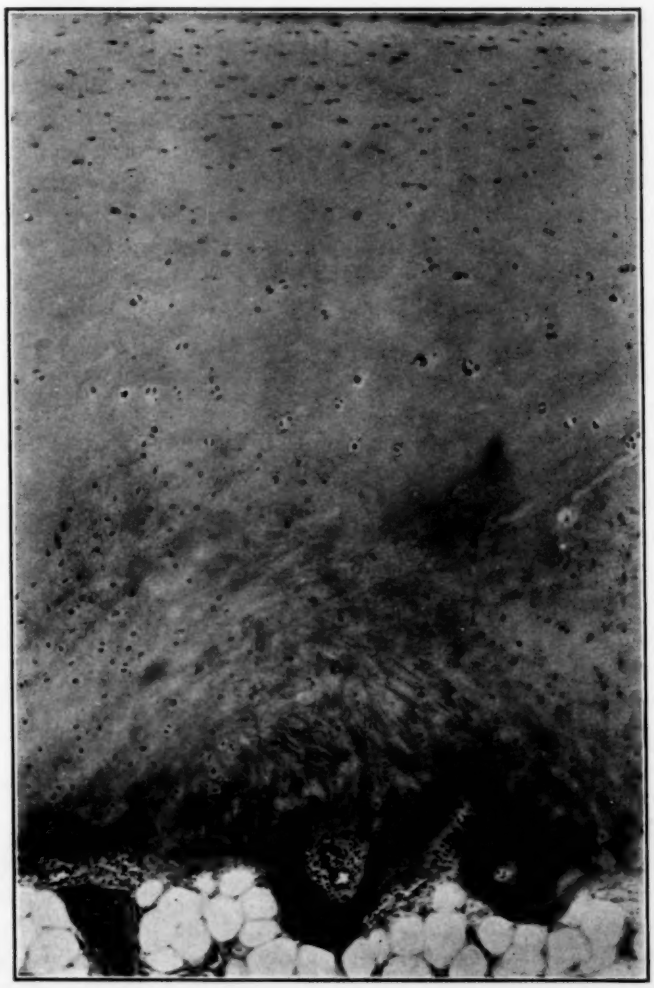

Fig. 10 (case 1).—Head of the humerus, enlarged about 75 times. Note the fibrous degeneration of the lower half of the joint cartilage. Note also the necrosis of a great number of cartilage cells within the fibrous area and the even more general necrosis in the neighboring hyaline cartilage.

but some having their spherical shapes intact. The picture was that of dense fibrous cartilage similar to a semilunar cartilage. This fibrous zone gradually blended into the more superficial layers, in the hyaline ground substance of which the collagenous fibers were firmly anchored.

A number of the freed cartilage cells proliferated and formed cellular areas. The superficial layers showed an unusually large number of necrotic cells close to the borderline between fibrous and hyaline cartilages.

It is a question to what this most unusual change of hyaline joint cartilage can be attributed. It certainly was not one of the more common damages of joint cartilage, caused by ultraphysiologic pressure or by disuse. There was little to suggest a more severe trauma which might have caused a sudden and strong compression of the cartilage, although I have seen a similar picture in the fractured head of a femur,[7] and in that instance there was no doubt that a sudden compression, probably taking place at the moment when the fracture occurred, had altered the structure of the traumatized cartilage so severely that it appeared fibrous. The histologic picture could, again, suggest a nutritional deficiency of the joint cartilage, which resulted in the decomposition of the hyaline cement substance. The aforementioned softening of portions of the pressure layer and edema of the ground substance may be preceding stages of such decomposition.

Summarizing, I may say that joint cartilage in cases of late rickets presents a number of interesting changes which partly are associated symptoms of the general atrophy of the skeleton; in part, however, they seem to be due to an intrinsic nutritional disorder. How far the specific rachitic damage of joint cartilage goes is, of course, hard to determine by simple histologic examination. Edema and decomposition of hyaline ground substance are apparently direct consequences of avitaminosis, as is also the lack of cartilage calcification and enchondral ossification. The extreme atrophy of the joint cartilage may in part be due directly to the rachitic process and to the general hypoplasia connected with it; in part, however, it represents a nonspecific change caused by inactivity of the joints.

One has become accustomed since publication of the work of Mikulicz to attribute static deformities of the lower extremities to a late rachitic process occurring during adolescence. Irregularities in the epiphysial plates, especially of the lower end of the femur and the upper end of the tibia, with inequality of growth caused by the disturbance of enchondral ossification, may explain a number of occurrences of genu valgum or genu varum. However, one should also consider the faulty enchondral ossification of the joint cartilage as a possible source of deformity. There is no doubt that the bony epiphyses grow by enchondral ossification of joint cartilage, and even a small irregularity or imbalance in this process must necessarily lead to disalinement of the extremity. Owing to the relative slowness of ossification of joint carti-

7. Freund, E.: Virchows Arch. f. path. Anat. **277**:326, 1930.

lage it is hard to evaluate such changes correctly, but the smallness of the epiphyses after the occurrence of rickets in childhood suggests that cessation of enchondral ossification of the joint cartilage occurred while the diaphysis continued to grow. I pointed out in a recent article the great importance of enchondral ossification of the joint cartilage for the acquisition of the final normal shape of the joint ends. In the case of a spastic idiot with joint contractures considerable deformities of the epiphyses had developed owing to slow or inactive enchondral ossification of those portions of the joint which were out of contact with the antagonist. The joint cartilage in these areas was atrophic and underwent absorption. Large defects in the end of the joint were thus able to develop. Similar deformities may result from inactivity and slowness of enchondral ossification in cases of severe late rickets. The imbalance of enchondral ossification of the joint cartilage explains many other deformities, especially congenital, for instance, clubfoot and dislocation of the hip. There is no doubt that enchondral ossification of joint cartilage is of far greater importance for the future shape of the extremity than it has been considered.

TREATMENT OF POSTOPERATIVE PARATHYROID INSUFFICIENCY WITH DISSOLVED CALCIUM LACTATE

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Parathyroid insufficiency is fortunately a comparatively rare complication following surgical treatment of the thyroid gland. Boothby [1] stated that 88 patients with this condition were treated at the Mayo Clinic between 1924 and 1929. This included patients operated on elsewhere as well as persons from the group on whom 13,300 thyroidectomies were performed at the clinic during this period. Because of the possibility of its occurrence, however, every surgeon should be familiar with the treatment of the condition.

MacCallum and Voegtlin in 1909 advanced the hypothesis that parathyroid tetany is due to a withdrawal of soluble and physiologically available calcium salts from the blood and especially from the nervous system. More recently McLean, Barnes and Hastings [2] have shown that the parathyroid glands control the concentration of the calcium ions in the blood plasma. Various methods of treatment have been reported, the most common being the use of various calcium salts, cod liver oil (or some form of vitamin D) and parathyroid extract. The basic principle of all methods of treatment is to supply the deficiency of usable calcium in the blood plasma.

Calcium lactate is the calcium salt most frequently used in the treatment of postoperative parathyroid insufficiency. Excellent results have been reported by Boothby as following the administration of cod liver oil and of calcium lactate dissolved in water. He stated that it is rarely necessary to give parathyroid extract or intravenous injections of calcium.

From the Starling-Loving University Hospital, Ohio State University.

1. (*a*) Boothby, W. M.: A Case of Parathyroid Insufficiency, Proc. Staff Meet., Mayo Clin. **7**:361-363, 1932; (*b*) Treatment of Postoperative Parathyroid Deficiency, ibid. **10**:87-91, 1935. (*c*) Boothby, W. M., and Davis, A. C.: Treatment of Postoperative Parathyroid Insufficiency, Arch. Int. Med. **58**:160-184, (July) 1936. (*d*) Boothby, W. M.; Haines, S. F., and Pemberton, J. de J.: Postoperative Parathyroid Insufficiency, Am. J. M. Sc. **181**:81-96, 1931.

2. McLean, F. C.; Barnes, B. O., and Hastings, A. B.: Influence of Thyro-Para-Thyroidectomy and a Parathyroid Hormone upon the State of Calcium in Serum of the Cat, Proc. Soc. Exper. Biol. & Med. **32**:253-255, 1934; The Relation of the Parathyroid Hormone to the State of Calcium in the Blood, Am. J. Physiol. **113**:141-149, 1935.

A review of the available experimental and clinical observations reveals a vast difference of opinion as to the effect of the oral administration of calcium lactate on the calcium content of the serum. Halverson, Mohler and Bergeim [3] studied the calcium content of human blood serum and the effect of the administration of calcium lactate in normal persons and in patients with pathologic conditions. The method of oral administration of calcium lactate is not stated. An elevation of only a milligram or less was observed even after administration of 5 Gm. daily. Voegtlin [4] stated that the oral administration of calcium is of doubtful value. Clark [5] found calcium lactate to be the only calcium salt acceptable by animals. The feeding of a diet containing 2 per cent of calcium lactate had no effect on the calcium content of the blood. Denis and Minot [6] gave 6 Gm. of calcium daily for a period of six to ten days to normal persons and produced no elevation of the calcium content of the plasma. Only daily determinations were made. In some cases they were able to raise the calcium content of the plasma in cats and rabbits when the initial concentration was low.

Luckhardt and Goldberg [7] were the first to report an elevation in the plasma calcium after oral administration of calcium lactate. They were able to preserve the lives of parathyroidectomized dogs by the administration by stomach tube of 10 Gm. of calcium lactate twice daily, dissolved or partially suspended in water, and 20 Gm. daily, ground in meat. They stated definitely that their article was written because of previous reports that oral administration of calcium salts was without benefit and that it seemed absurd to give enormous quantities of calcium daily by venoclysis. The importance of dissolving the calcium lactate was apparently not realized. Jansen [8] reported no elevation in the

3. Halverson, J. O.; Mohler, H. K., and Bergeim, O.: The Calcium Content of the Blood Serum in Certain Pathological Conditions, J. Biol. Chem. **32**:171-179, 1917.

4. Voegtlin, C.: The Physiological and Pathological Importance of the Parathyroid Gland from the Experimental Aspect, Surg., Gynec. & Obst. **25**:244-249, 1917.

5. Clark, G. W.: Effect of Hypodermic and Oral Administration of Calcium Salts on the Calcium Content of Rabbit Blood, J. Biol. Chem. **43**:89-95, 1920.

6. Denis, W., and Minot, A. S.: Effects of Feeding with Calcium Salts on the Calcium Content of the Blood, J. Biol. Chem. **41**:357-361, 1920.

7. (*a*) Luckhardt, A. B., and Goldberg, B.: Preservation of the Life of Parathyroidectomized Dogs, by Means of Oral Administration of Calcium Lactate, J. A. M. A. **80**:79-80 (Jan. 13) 1923. (*b*) Luckhardt, A. B., and Blumerstock, J.: Additional Observations on Completely Thyroparathyroidectomized Dogs, Am. J. Physiol. **63**:409-410, 1922-1923.

8. Jansen, W. H.: Kalkstoffwechsel, Blutkalkgehalt und Kalkwirkung, Klin. Wchnschr. **3**:715-719, 1924.

calcium content of the blood after the administration of calcium lactate. Hjort [9] found that calcium lactate given by stomach tube in 5 per cent solution produced an increase of 17.4 to 48.2 per cent in the calcium content of the serum of normal dogs, the maximum elevation occurring from one to two hours after the administration. He also used thyroparathyroidectomized dogs, and the results were the same except in the tendency to slower return to the preingestive calcium values. He explained the failure of others on the basis of too small doses and the drawing of blood after the calcium content had returned to normal. Kahn and Roe [10a] gave calcium lactate dissolved in water in doses of 5 and 20 Gm. and produced a marked elevation of the calcium content of the serum, the average being 81 per cent. The maximum rise occurred from four to seven hours after the oral administration. The return of the blood to normal was not proportional to the dose. The serum calcium returned to normal in about fourteen hours. Bauer and Ropes [11] criticized severely the results of Kahn and Roe. The average elevation of serum calcium they obtained was 14 per cent with a dose of 10 Gm. Their method of administration was different in that they gave the calcium lactate followed by water and not dissolved in water. Roe and Kahn [10b] reported that calcium lactate given to normal subjects produced a marked rise in the calcium content of the serum, a dose of 5 Gm. producing as marked a rise as did a dose of 20 Gm. and also producing an elevation sustained for a longer period. The elevation was not obtained when the calcium lactate was given in milk, a carbohydrate or a protein. They did not realize the importance of dissolving the calcium but concluded that calcium lactate should be given before meals, as food hinders the absorption. They further concluded that it is not necessary to incur the dangers of intravenous medication with calcium. Boothby stated that calcium lactate is not effective in the treatment of parathyroid insufficiency when given dry or in an emulsion and seems to be nearly valueless when given in tablet form.

An analysis of the results obtained reveals that an elevation in the calcium content of the serum has been obtained by oral administration only when the calcium lactate was dissolved in water. This fact has not been recognized by many and has not been emphasized in any investi-

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9. Hjort, A. M.: The Influence of Orally Administered Calcium Salts on the Serum Calcium of Normal and Thyroparathyroprivic Dogs, J. Biol. Chem. **65:** 783-795, 1925.

10. (*a*) Kahn, B. S., and Roe, J. H.: Calcium Absorption from the Intestinal Tract in Human Subjects, J. A. M. A. **86:**1761-1763 (June 5) 1926. (*b*) Roe, J. H., and Kahn, B. S.: Absorption of Calcium from the Intestinal Tract of Human Subjects: The Influence of Foods, ibid. **88:**980-984 (March 26) 1927.

11. Bauer, W., and Ropes, M. W.: The Effect of Calcium Lactate Ingestion on Serum Calcium, J. A. M. A. **87:**1902-1904 (Dec. 4) 1926.

gative work. Because of this fact patients are of necessity subjected to intravenous injections of calcium and to indiscriminate use of parathyroid extract.

On the basis of investigative work, calcium lactate is the calcium salt of choice for oral administration. There is no change in the p_H of the blood when dissolved calcium lactate is used.[12] Calcium chloride causes depression and loss of appetite. Hjort reported the effects of calcium chloride, calcium lactate, calcium glycerophosphate, calcium carbonate and calcium bicarbonate on the calcium content of the serum when dissolved and when given orally. Calcium chloride caused an increase of 32.1 per cent in the calcium content of the serum but was not satisfactory because of gastric irritation and vomiting. Calcium glycerophosphate and calcium carbonate were less effective than calcium lactate. Calcium bicarbonate produced no elevation.

The following case illustrates the failure to relieve the tetany of parathyroid insufficiency when the calcium salts were not dissolved and the success in relieving symptoms when calcium lactate was dissolved in water.

REPORT OF CASE

B. S., a white woman aged 30, was admitted to the University Hospital with the complaint of continuous vaginal bleeding which had begun about two years prior to admission, after the delivery of her fifth child. She also complained of orthopnea, swelling of the feet and ankles and shortness of breath on mild exertion, all of about one year's duration. She had had nocturnal dyspnea for two months. There had been a progressive loss of 45 pounds (20.4 Kg.) in weight in eight months. The patient was well developed and well nourished and was not acutely ill. Slight exophthalmos was present. The thyroid gland was visibly enlarged. No palpable nodules were present. The lungs were normal. The blood pressure was 140 systolic and 60 diastolic. At the mitral, pulmonic and aortic areas there was a soft, nontransmitted systolic murmur. The abdomen was normal. There was no edema of the extremities. A pelvic examination revealed acute tenderness in both the right and the left adnexa. A diagnosis of chronic inflammation of the pelvis and toxic diffuse hyperplastic goiter was made.

A roentgenogram of the neck showed a left lateral deviation of the trachea. The basal metabolic rate was plus 38. Iodine in the form of potassium iodide was given preparatory to operation.

A subtotal thyroidectomy was done with the patient under anesthesia induced by avertin with amylene hydrate and nitrous oxide. The goiter removed weighed 90 Gm. It contained a few nodules of sizes up to 3 cm. in diameter and was largely of the diffuse hyperplastic variety, showing extensive iodine-induced colloid remission. A diagnosis of hyperplastic nodular colloid goiter was made. No parathyroid tissue was found on repeated examinations.

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12. Salversen, H. A.; Hastings, A. B., and McIntosh, J. F.: The Effect of the Administration of Calcium Salts on the Inorganic Composition of the Blood, J. Biol. Chem. **60**:327-339, 1924. Seyle, H.: On the Stimulation of New Bone Formation with Parathyroid Extract and Irradiated Ergosterol, Endocrinology **16**:547-558, 1932.

The immediate postoperative condition was good. Seventeen hours after operation the patient noticed tingling sensations in the arms, the hands and the feet. The hands were drawn in typical tetanic position. The Chvostek and Trousseau signs were present. The calcium content of the blood serum was 8 mg. per hundred cubic centimeters and the inorganic phosphorus content 3.7 mg. Fifteen grains (1 Gm.) of calcium gluconate was given intravenously and produced relief. Six hours later symptoms again appeared and were relieved with the same treatment. On the second day after the operation the patient had mild tingling sensations of the hands, the feet and the face. Daily doses of 60 grains (4 Gm.) of calcium gluconate in tablet form were started. On the third day she again had tetanic spasms of the hands, the feet and the face. Intravenous calcium gluconate had to be used to obtain relief, and the same measure was necessary again on the fourth day, even with the oral administration of either calcium gluconate or calcium lactate in milk or in tablet form. On the fifth day the calcium content of the serum was 7 mg. and the inorganic phosphorus content 8 mg.

On the seventh day the patient again had tetanic spasms of the hands and arms. Thirty grains (2 Gm.) of calcium lactate was dissolved in water and given orally. Relief was obtained as quickly as with intravenous therapy. The following day 90 grains (6 Gm.) of dissolved calcium lactate was given; purified vitamin D in propylene glycol (drisdol) was also given. The Chvostek and Trousseau signs were still present, but the patient had no complaints. She remained in the hospital three days longer, being given 180 grains (12 Gm.) of dissolved calcium lactate and 5 drops of drisdol daily. She had no further seizures or complaints. Daily determinations of the calcium content of the serum ranged from 6.1 to 7.4 mg., and the inorganic phosphorus content increased from 3 to 5.5 mg., all determinations being made twelve hours after administration of the evening dose of calcium lactate.

She was dismissed on the eleventh day with instructions to continue the use of dissolved calcium lactate and drisdol. A week later she did a large washing without any ill effects.

On the seventeenth day she was instructed to go as long as possible without calcium or the vitamin D preparation. In twenty-four hours she had severe tetanic spasms, which were relieved with dissolved calcium lactate. In the next six days she had a few spasms but gradually became adjusted to the lack of calcium. On the forty-second day after the operation the calcium content of the serum was 6.5 mg. and the inorganic phosphorus content 4.3 mg. The basal metabolic rate was minus 13. Chvostek's sign was present in slight degree.

Because of the possibility of cataract formation and other sequelae of parathyroid insufficiency, administration of 180 grains (12 Gm.) of dissolved calcium lactate and 5 drops of drisdol was again instituted as daily treatment.

The patient had severe tetanic seizures during an infection of the upper respiratory tract, which were relieved with dissolved calcium lactate. The following day she was given 50 units of solution of parathyroid U. S. P. (in the form of parathyroid extract-Lilly). She suffered no other attacks but still complained of vaginal bleeding.

Four months after the onset of parathyroid insufficiency she was doing farm work and taking care of a bedfast patient. No apparent discomfort was noted.

Because of continued vaginal bleeding and the resulting secondary anemia she was transferred to the gynecologic service, and a hysterectomy was done by Dr. P. J. Reel. A pathologic diagnosis was made of chronic endocervicitis, chronic

salpingitis and lutean stimulation of the endometrium. The postoperative period was normal under the following regimen: parathyroid extract and dissolved calcium lactate preoperatively, parathyroid extract and Ringer's solution the day of operation and the first day after the operation and dissolved calcium lactate and drisdol by mouth beginning on the fourth day after the operation.

One year after the onset of parathyroid insufficiency the patient was still doing farm work. The secondary anemia had gradually disappeared. The calcium content remained unchanged from the previous low levels.

COMMENT

This case shows the advantages of administration of dissolved calcium lactate after failure of calcium salts given in tablet form or in milk. Previous to the administration of dissolved calcium lactate, intravenous calcium gluconate had to be given. The patient was able to leave the hospital under this type of treatment, returning from time to time for observation.

During the period in which calcium therapy was gradually withdrawn from the patient she did have a return of symptoms, but there was a gradual adjustment to the low calcium level of the blood serum. Because of the fact that experimental and clinical experience has shown that cataracts and other untoward symptoms may develop,[13] it was considered advisable to continue the treatment. Later a successful major operation was done, and the postoperative convalescence was normal.

McLean, Barnes and Hastings concluded that the function of the parathyroid gland is to supply the calcium ions in the blood plasma and that in the presence of parathyroid insufficiency the calcium ion concentration is lowered. It is probable that calcium lactate when given in the dissolved state supplies this deficiency. The absorption of the calcium ions must be fairly rapid, as symptoms of tetany in this case were relieved in fifteen to thirty minutes.

Tetany occurred during an infection of the upper respiratory tract which is a frequent occurrence in such cases.[14]

The administration of vitamin D is as important as the administration of calcium. Brougher[15] reported 4 cases of postoperative parathyroid insufficiency in which cod liver oil relieved all symptoms. Boothby and Davis[1c] in a recent review of the treatment of postoperative parathyroid insufficiency gave an excellent review of the rationale of vitamin D therapy and emphasized the difficulty in determining the

13. Cole, L.: Parathyroid Tetany and Cataract, Lancet **1**:13-16, 1930. Boothby.[1a] Luckhardt and Blumerstock.[7b]

14. McGhie, A. B.: Parathyroid Disturbances Following Thyroidectomy, with Report of a Case, Canad. M. A. J. **31**:27-29, 1934.

15. Brougher, J. C.: Viosterol (Irradiated Ergosterol) in the Treatment of Parathyroid Tetany, J. A. M. A. **94**:471-473 (Feb. 15) 1930.

dosage. The vitamin increases the absorption or decreases the excretion in the intestines, thus tending to produce a positive calcium balance.[16]

In some cases occasional injections of parathyroid extract have to be used in addition to cod liver oil and dissolved calcium lactate.[1b] Continued injections are not effective, as the patient acquires a tolerance to the drug. There is an initial rise in the calcium content of the serum.[17] Elimination of calcium is also increased. Pugsley and Seyle [18] reported the histologic picture of bone after injections of parathyroid extract. With the rise in serum calcium there are large numbers of osteoclasts, or bone-destroying cells, in the bone marrow. With continued injections these cells disappear and are replaced by osteoblasts. Formation of bone occurs, and during this process there is no elevation in the calcium content of the serum. This explains the tolerance to the parathyroid extract. With the use of calcium lactate there are retention of inorganic phosphorus and a diminished urinary excretion of phosphorus, even for normal persons.[19] It has been shown that parathyroid extract causes an immediate phosphorus diuresis and a decrease in the inorganic phosphorus content of the serum of normal persons and of patients with parathyroid insufficiency.[20] This is probably another indication for occasional injections of the extract.

SUMMARY

A review of the literature is presented as to the effect of calcium salts, particularly calcium lactate, when given orally, on the calcium content of the blood serum of normal persons and of patients with para-

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17. Collip, J. B.: The Extraction of a Parathyroid Hormone Which Will Prevent or Control Parathyroid Tetany and Which Regulates the Level of Blood Calcium, J. Biol. Chem. **63**:395-438, 1925. Collip, J. B.; Clark, E. P., and Scott, J. W.: The Effect of Parathyroid Hormone on Normal Animals, ibid. **63**:439-460, 1925.

18. Pugsley, L. I., and Seyle, H.: The Histological Changes in the Bone Responsible for the Action of Parathyroid Hormone on the Calcium Metabolism of the Rat, J. Physiol. **79**:113-117, 1933.

19. Heyl, F. W., and Hart, M. C.: The Availability of the Calcium in Calcium Lactate in the Human, J. Am. Pharm. A. **17**:225-232, 1928. Robinson, C. S.; Huffman, C. F., and Mason, M. F.: The Results of the Ingestion of Certain Calcium Salts and of Lactose, J. Biol. Chem. **84**:257 267, 1929.

20. Ellsworth, R.: Action of Parathyroid Extract on the Renal Threshold for Phosphorus, J. Clin. Investigation **11**:1011-1017, 1932. Goadby, H. K., and Stacey, R. S.: On the Action of Parathormone, Biochem. J. **28**:2092-2094, 1934; **30**:269-272, 1936.

thyroid insufficiency. Only dissolved calcium salts produce any marked elevation in the calcium content of the serum. Calcium lactate when dissolved in water and given orally produces a marked elevation.

A case of severe postoperative parathyroid insufficiency is discussed in which calcium salts in tablet form or in milk did not relieve tetany. Calcium lactate dissolved in water gave immediate relief of symptoms. A major operation was done eight months after the onset of parathyroid insufficiency. Satisfactory medical management of the condition resulted in a normal postoperative convalescence.

The staff of the Division of Gynecology, Department of Surgery, and the staff of the Department of Surgical Research permitted me to follow the case reported in this paper. The staff of the Department of Surgical Research gave technical assistance in determining the values for phosphorus and calcium.

MECHANICAL INTESTINAL OBSTRUCTION COMPLICATING PELVIC INFLAMMATORY DISEASE

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Intestinal obstruction caused by gynecologic disease is infrequent. Reports of obstruction due to strangulation of the intestine by a cyst pedicle, to hernia into the broad ligament or to endometriosis have been found. There have been few reports of intestinal obstruction associated with pelvic inflammatory disease; the following discussion will be confined solely to this particular complication.

McIver stated that tubal inflammation may result in intestinal obstruction.[1] However, in review of 21 cases of obstruction caused by bands (without previous laparotomy), he cited no case in which pelvic inflammatory disease was the cause.[2] Treves [3] wrote, "I have knowledge of several instances in which 'pelvic inflammation,' 'meritis,' or 'pelvic cellulitis,' appears without doubt to have provided the band." Norris,[4] in his treatise "Gonorrhea in Women," did not even mention intestinal obstruction as a complication. Kaufman [5] reported a single case of ileus complicating salpingitis. Vanderzypen [6] and Martens [7] have each reported 2 cases, and Thaler [8] 3 similar cases. Holtz,[9] in 1,262 cases

From the gynecologic service of the Harlem Hospital, H. C. Falk, M.D., Director.

1. McIver, M. A.: Acute Intestinal Obstruction, New York, Paul B. Hoeber, Inc., 1934.
2. McIver, M. A.: Acute Intestinal Obstruction, Arch. Surg. **25:** 1106 (Dec.) 1932.
3. Treves, F.: Intestinal Obstruction, Baltimore, William Wood & Company, 1889.
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5. Kaufman, M. R.: Occlusion intestinale aiguë, Gynécologie **29:** 603, 1930.
6. Vanderzypen: L'occlusion intestinale d'origine gynécologique, Bruxelles-méd. **16:** 800, 1936.
7. Martens, M.: Ueber mechanischen Ileus bei acut-entzündlichen abdominal Erkrankungen, Deutsche Ztschr. f. Chir. **86:** 508, 1907.
8. Thaler, H.: Die entzündlichen Adnex-und Bindegewebserkrankungen, Arch. f. Gynäk. **93:** 413, 1911.
9. Holtz, F.: Klinische Studien über die nicht tuberkulöse Salpingo-oophoritis, Acta obst. et gynec. Scandinav. (supp.) **10:** 1, 1930.

of tuberculous salpingo-oophoritis, found only 1 case of intestinal obstruction. Flesch-Thebesius [10] in 162 cases of mechanical ileus due to adhesions found the condition to be of gynecologic origin in 15; in 8 it was caused by parametritis, and in 7, by salpingitis. Turunen [11] reported 12 occurrences of mechanical ileus in 3,025 cases of adnexitis caused by abortion, by infection during delivery or by gonorrhea. Of these, 10 occurrences were due to stringlike adhesions, and 2 were caused by agglutination of loops of intestine. Usually the complication occurred after long-standing inflammation; in only 2 cases had the symptoms of pelvic inflammatory disease been present for less than one month. The mortality in this series was 47.7 per cent.

Mechanical intestinal obstruction complicating pelvic inflammatory disease is uncommon, but it does occur. In an active gynecologic service to which approximately 60 per cent of all admissions are for pelvic infection, either postabortal or gonorrheal, attention was called to this complication by its occurrence in 2 cases within one month. An additional case was found in the hospital records of ten years ago.

REPORT OF CASES

CASE 1.—A. C., a Negress aged 42, married, was first admitted to the hospital on Oct. 14, 1927. She was a bipara and had had five pregnancies. She complained of pain in the abdomen, which had begun suddenly four days previously and had become progressively worse. Pain in the chest had been present for the past day. The menses began at the age of 13; they were regular, and the periods lasted three days. The date of the last period was uncertain, although the patient said she was not pregnant. She had had an abortion fourteen years before. The temperature was 105 F., the pulse rate 160 and the respiratory rate 34. The patient appeared prostrated and showed indefinite signs of consolidation in the chest (which rapidly cleared). The abdomen was distended and tympanitic. Tenderness, rebound and rigidity were present, particularly in the left hypogastrium. Vaginal examination showed the cervix to be cone shaped and flattened; the external os was closed. The fundus of the uterus was small and anterior. A large mass was felt in both cul-de-sacs, extending upward to an indefinite point near the umbilicus. The white blood cell count was 24,000, with 96 per cent of polymorphonuclears. A diagnosis of postabortal pelvic cellulitis was made.

The temperature ranged up to 103 F. for three days, after which softening occurred. Colpotomy was then performed, with evacuation of a large amount of pus. Despite the colpotomy, the temperature did not return to normal until the twenty-eighth day after the operation. During this period, digital dilation of the colpotomy opening, injections of milk given intramuscularly and vaginal diathermy were used, with gradual subsidence of the parametrial masses. On the forty-fourth day after the operation the patient appeared well; the temperature was

10. Flesch-Thebesius, M.: Ueber Ileus durch Verwachsungen und Stränge, Deutsche Ztschr. f. Chir. **157:** 60, 1920.

11. Turunen, A. O.: Ueber den Darmverschluss als Komplikation von Krankheiten und Operationen der inneren Geburtsteile, Acta obst. et gynec. Scandinav. **12:** 421, 1932.

normal, no symptoms were present and there were no physical signs except for slight induration in the fornices. On this day there was a sudden onset of colicky abdominal pain, vomiting and generalized rigidity, with tenderness at McBurney's point. The white blood cell count was 21,000, with 90 per cent of polymorphonuclears. Enemas were not effectual. On the following day, the patient appeared worse; pain and vomiting continued, and she was operated on. The preoperative diagnosis was mechanical intestinal obstruction.

At operation, 300 cc. of straw-colored fluid was found in the abdomen. The small intestine was distended and injected. The loops were followed until a loop of the lower part of the ileum was found to be bound down to the broad ligament and to be kinked at this point. Below the kink the intestines were collapsed. The pelvic peritoneum and the pelvic organs appeared to be normal. The adherent kinked loop of intestine was freed from the broad ligament, and the distal portion of the intestine immediately ballooned out with gas. The patient made an uneventful recovery and was discharged on the twenty-sixth day after the operation (Dec. 23, 1927).

Case 2.—M. B., a Negress aged 16, single, was first admitted to the hospital on Nov. 25, 1936, complaining of pain in the abdomen for the past five weeks, accompanied by vaginal discharge, burning on urination, frequent voiding and nocturia. The pain was most pronounced in the right lower quadrant of the abdomen. It began immediately after a menstrual period five weeks before her admission. She vomited several times the night before admission. The menses began at the age of 11; they were regular; the periods lasted four days and were unaccompanied by pain. The last normal period was one week before admission. The temperature was 98.6 F., the pulse rate 80 and the respiratory rate 24. The patient appeared moderately ill. The abdomen was soft, and tenderness was present in both lower quadrants. There was no distention, no rigidity and no rebound. Vaginal examination showed the uterus to be anteverted; a tender sausage-shaped mass was present in each fornix. The white blood cell count at this time was 21,000, with 80 per cent of polymorphonuclears. The impression was that a bilateral pyosalpinx existed with moderate pelvic peritonitis. An enema given in the evening of the same day was effectual.

For four days the temperature was below 100 F. On the fifth day, the temperature rose to 100.4 F. and the patient suddenly appeared acutely ill. The abdomen was diffusely tender and was distended. It was thought at this time that peritonitis due to a leaking pyosalpinx was present. An enema returned fluid stained with fecal material, but no gas. The distention, tenderness, vomiting and rigidity increased in severity. A Harris drip instituted at this time was ineffectual. The temperature rose to 101.6 F. just before death, and the patient died eight days after admission (Dec. 3, 1936), four days after the occurrence of what was interpreted as being a "leaking tube" with peritonitis.

Autopsy revealed nothing abnormal except in the abdomen. A loop of ileum was pulled down, bound and kinked by a fibrous adhesion which extended from the serosal surface of a loop of intestine to the posterior wall of the pelvis, in the region of the sacrum—about 6 inches (15 cm.) of the ileum was bound down firmly and completely obstructed by this adhesion. The small intestine proximal to the adhesion was dilated; the intestine below the adhesion was collapsed. The adhesion itself was grayish and vascular and measured 2 inches (5 cm.) in length and 3 inches (7.5 cm.) in thickness. Numerous rather firm adhesions were present in the pelvis, which bound the uterus and tube to the bladder and rectum. There were also fine adhesions between the liver and the

diaphragm; these were of the "violin string" type. There was a right pyosalpinx, and the ovaries appeared normal. The diagnosis was fibrous adhesion extending from the serosa of the ileum to the anterior wall of the sacrum; strangulation of the ileum; right pyosalpinx; pelvic adhesions; perihepatitis; dehydration. The cause of death was acute mechanical intestinal obstruction.

CASE 3.—J. B., a nulliparous Negress aged 19, single, was first admitted to the hospital on Nov. 16, 1936. She complained of pain in the lower part of the abdomen and in the back for two weeks, associated with vaginal discharge for ten days. These symptoms became progressively more severe and were associated with fever. No vomiting occurred. There was a history of an abortion two years previously. The menses began at the age of 13; they were regular, and the periods lasted four days. The last normal period was seventeen days prior to admission. On the day of admission to the hospital the menses reappeared; this period was nine days earlier than usual. The temperature was 101 F., the pulse rate 108 and the respiratory rate 24. The patient appeared acutely ill and complained of severe pain in the lower part of the abdomen. The abdomen was rigid. Tenderness and rebound were present in both lower quadrants. Vaginal examination showed the cervix to be short, conical and closed; a brownish, bloody discharge was present. Pain was elicited on movement of the cervix. The uterus was small and retroverted, and there was an extremely tender sausage-shaped mass in each fornix, closely applied to the uterus. The white blood cell count was 9,960, with 84 per cent of polymorphonuclears. The sedimentation rate was 18 mm. in twenty minutes. The diagnosis was bilateral pyosalpinx, pelvic peritonitis and retroversion of the uterus.

With palliative therapy, the patient's temperature ranged between 100 and 102.4 F. for one week. The temperature thereafter was constantly below 100 F., the abdominal signs subsided and the patient was apparently recovering. She was allowed to be out of bed on the sixteenth day; that evening she had a sudden recurrence of symptoms, with abdominal pain and vomiting. There was moderate tenderness and rigidity in the lower part of the abdomen; an enema was effectual. On the following day (the seventeenth day of hospitalization), she continued to vomit and to complain of cramplike pain. The temperature was 100 F.; the lower part of the abdomen was distended, tympanitic, tender and rigid. Because of the sudden onset of cramplike pain, mechanical obstruction was suspected, rather than paralytic ileus caused by recurrence of the peritonitis. A Harris drip was given, and liquid petrolatum was introduced into the duodenum by means of a Levine tube. No oil, gas or feces was recovered in the Harris drip in twelve hours. A flat roentgenogram of the abdomen taken on the same day showed distended loops of small bowel (with fluid levels) and no evidence of gas in the large intestine. The diagnosis of mechanical obstruction of the small bowel was thus confirmed, and a laparotomy was performed that evening. At operation, 20 cc. of free straw-colored, odorless fluid was found in the peritoneum. There were many fresh fibrinous adhesions between loops of ileum, resembling violin strings. The small intestine was distended and somewhat congested. The distended loops were followed toward the cecum until a firm adhesion band was found 4 inches (10 cm.) proximal to the ileocecal junction, causing complete occlusion of a loop of ileum. This band ran from the serosa of the ileum to the pelvis; distal to the band the ileum was completely collapsed. As soon as the adhesion was severed the collapsed intestine ballooned out. The pelvic organs were rapidly palpated, and the adnexa were found to be subacutely inflamed. The patient made an uneventful recovery and was discharged on December 26, the eighteenth day after the operation. An examination of the pelvis at this time revealed small, slightly tender masses in each fornix.

ETIOLOGY AND PATHOGENESIS

The fundamental methods by which bands of adhesions produce strangulation are well known. McIver [1] stated:

> Bands form bridges or arches under which intestinal loops become engaged or strangulated, or long cords are formed into nooses or knots which capture a loop. Of these two types, strangulation under bands is more frequent. All that is essential for strangulation is a firm band attached at two points to form an arch and a firm surface to make the floor of the arch.

Bands are congenital or inflammatory in origin. Primary inflammatory bands (without previous laparotomy) are rarely seen today, since they are the result of peritonitis following appendicitis or ruptured gastric ulcer; in such cases the condition is usually diagnosed early, and the patient is operated on before firm adhesions form. However, pelvic peritonitis, for which the usual treatment is conservative and operation is deferred, presents favorable opportunity for the formation of inflammatory bands. Treves stated:

> Where the isolated adhesion is due to pelvic peritonitis, it may be found to be attached by one end to some pelvic viscus and by the other to a neighboring part. Thus bands are found passing from the uterus, ovary or bladder to the parietal peritoneum of the pelvis or abdomen; or starting from the same source, they may attach themselves to the cecum or sigmoid flexure, or with much greater frequency to some part of the lower ileum or its mesentery. In several instances, the constricting band has merely passed from one point on the pelvic wall to another.

The occurrence of adhesive bands after acute salpingitis has not been generally recognized. Another fact frequently overlooked is that the accompanying primary peritonitis may be widespread. Curtis [12] has described violin string adhesions about the liver in cases of chronic salpingitis; he stated the opinion that these adhesions are the end result of acute inflammation. Fitz-Hugh [13] has recovered the gonococcus from the drainage tract after a laparotomy for acute perihepatitis. Therefore, since it is recognized that salpingitis may cause pelvic and generalized peritonitis with the secondary formation of bands, it can readily be seen how mechanical intestinal obstruction may occur. Falk [14] has shown that general peritonitis may be caused by postabortal infection by direct extension through the tubes. In such a case the condition is usually of streptococcic origin and results in death within two to

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12. Curtis, A. H.: (*a*) Adhesions of the Anterior Surface of the Liver, J. A. M. A. **99**: 2010 (Dec. 10) 1932; (*b*) Obstetrics and Gynecology, Philadelphia, W. B. Saunders Company, 1933, vol. 2, chap. 42, p. 448.

13. Fitz-Hugh, T., Jr.: Acute Gonococcic Peri-Hepatitis: A New Syndrome of Right Upper Quadrant Abdominal Pain in Young Women, Rev. Gastroenterol. **3**: 125, 1936.

14. Falk, H. C.: Abortion, Am. J. Surg. **35**: 187, 1937.

three weeks. This does not allow sufficient time for adhesions to form. However, in cases in which postabortal infection causes pelvic cellulitis, intra-abdominal adhesions may occur, although the condition is primarily extraperitoneal. The mechanism by which this is produced is believed to be as follows:

1. Subperitoneal cellulitis may cause edema of the peritoneum, with exudation on the peritoneal surface, resulting in a roughened peritoneum and in local peritonitis.[15]

2. Pelvic cellulitis may produce peritoneal blebs; pinpoint rupture of a bleb into the peritoneum may cause an adhesion to form at this site.

3. An imminent intraperitoneal perforation of an abscess of a broad ligament may be sealed off from the general peritoneal cavity by a loop of intestine becoming adherent at this point; evacuation of the abscess and healing of infection cause shrinkage of the swollen parametria, with the result that the adherent loop of intestine is drawn into the pelvis and kinked, causing obstruction.

4. The omentum may be drawn into the pelvis by one of the methods described and may act as a constricting band.

SYMPTOMS

The symptoms of this condition are like those of acute intestinal obstruction from any other cause. There is a sudden onset of vomiting, of distention and of cramplike pain, which is unlike the unremitting pain caused by salpingitis. If the complication is not recognized early, fecal vomiting and complete obstipation result. On roentgen examination of the abdomen the typical signs of mechanical obstruction may be seen, that is, "step ladder" pattern, gas and fluid levels in the small intestine and absence of gas in the large bowel. Obstruction occurring in pelvic inflammatory disease usually appears while the inflammatory process is subsiding. In 2 of our cases the obstruction occurred late, when both patients were recovering. In the other case, although the obstruction occurred shortly after admission to the hospital, the autopsy showed that the salpingitis was of long duration.

DIFFERENTIAL DIAGNOSIS

Paralytic ileus due to peritonitis must be differentiated from mechanical obstruction. This differentiation at times may be difficult, as both conditions manifest themselves by distention, tympanites, constipation, vomiting and signs of the underlying peritoneal inflammation. Diffuse

15. Polak, J. O.: Pelvic Inflammation in Women, Gynecological and Obstetrical Monograph Series, New York, D. Appleton and Company, 1924.

peritonitis in gynecologic disease most commonly is caused by acute salpingitis, by "leaking" pyosalpinx, by ruptured pyosalpinx or by septic abortion. Associated with these conditions we find elevated temperature and leukocytosis as well as the local signs of acute pelvic inflammation. On the other hand, the local and general symptoms of the acute inflammation have subsided or are subsiding when the acute intestinal obstruction occurs. When there is a sudden recurrence of acute symptoms, with cramplike pain, vomiting and distention, in a patient with pelvic inflammation who is apparently recovering, mechanical obstruction must be ruled out. All patients with ileus in this service are treated with duodenal drainage (Levine tube) and a Harris drip, for both diagnostic and therapeutic purposes. It has been found that with complete mechanical obstruction there is no gas or fecal return in the drip. With paralytic ileus the drip causes sufficient peristalsis to allow some return of fecal material and gas. A further refinement in the differential diagnosis is to introduce liquid petrolatum through the tube (eight doses of 4 drachms [14.4 cc.]) at intervals of one hour. With paralytic ileus some oil will be recovered in the drip; with mechanical obstruction no oil is recovered. A flat roentgenogram of the abdomen should always be taken for evidence of mechanical obstruction.

PROGNOSIS AND TREATMENT

The prognosis is in direct relation to the time elapsing between the occurrence of obstruction and its release. If operation is performed early a recovery usually results; if the condition is not recognized or if the operation is delayed a fatality is to be expected. It is particularly important for gynecologists to differentiate early between ileus caused by peritonitis of pelvic origin and that caused by mechanical obstruction. If mechanical obstruction is not recognized or is recognized late, the period of optimum operability is lost, for the treatment of this type of obstruction is immediate laparotomy, whereas the treatment of pelvic peritonitis is essentially nonoperative in the early stages. Surgical elimination of the pelvic inflammatory mass at this time would seem injudicious.

SUMMARY AND CONCLUSIONS

Three cases of intestinal obstruction complicating pelvic inflammatory disease are reported.

The pathogenesis of this complication is discussed.

The outstanding symptom of the complication has been found to be the sudden onset of cramplike pain and distention in a patient with pelvic inflammatory disease who is apparently recovering.

It is important to diagnose this complication promptly in order to insure early surgical intervention.

TUBERCULOSIS OF THE STOMACH

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Tuberculosis of the stomach is an inflammatory granulomatous lesion of the stomach produced by the tubercle bacillus. Little was known about this condition before 1824, when a case was reported by Barkhausen.[1] Since that time, however, the subject has aroused considerable interest, and 367 additional cases have been reported. This interest has been due partially to the rarity of the condition, but it also is largely attributable to the interesting clinical problems and varied pathologic manifestations presented by the condition.

Although Barkhausen was the first to report a case of gastric tuberculosis, the condition was not definitely established as a pathologic entity until Litten's [2] report and classic description of the findings in a case he had observed in 1876. Four years after the discovery of the tubercle bacillus by Koch in 1882, Coats [3] reported a case in which he was able to demonstrate the tubercle bacillus in the depths of the lesion. He thus became the first to report a proved instance of gastric tuberculosis. Since that time numerous reports of single cases and several extensive reviews of series of cases collected from the literature have been published. Notable among these have been the review by Arloing [4] in 1902, that by Ricard and Chevrier [5] in 1905, that by Broders [6] in 1917 and that by Good [7] in 1929.

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Abstract of thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in surgery.

1. Barkhausen, cited by Broders.[6]

2. Litten, M.: Ulcer ventriculi tuberculosum, Virchows Arch. f. path. Anat. **67**:615-617 (Aug.) 1876.

3. Coats, J.: On a Case of Tuberculosis of the Stomach, and One of Acute Miliary Tuberculosis Depending on Tuberculosis of a Pulmonary Vein, with Remarks on the Pathology of These Conditions, Glasgow M. J. **26**:53-61, 1886.

4. Arloing, F., cited by Broders.[6]

5. Ricard and Chevrier: De la tuberculose et des sténoses tuberculeuses du pylore, Rev. de chir., Paris **31**:557-586 (May) 1905.

6. Broders, A. C.: Tuberculosis of the Stomach, with a Report of a Case of Multiple Tuberculous Ulcers, Surg., Gynec. & Obst. **25**:490-498 (Oct.) 1917.

7. Good, R. W.: Tuberculosis of the Stomach: An Analysis of Cases Recently Reviewed, Arch. Surg. **22**:415-437 (March) 1931.

INCIDENCE

The incidence of tuberculosis of the stomach as determined at necropsy and by the examination of surgical material has varied considerably in the reports of different investigators. The most extensive investigation of the incidence of gastric tuberculosis at necropsy was that by Glaubitt.[8] In 1901 this investigator reported that he observed gastric tuberculosis in 47 of a series of 12,528 cases in which necropsy was performed. In 2,237 of these cases the patients had died of tuberculosis. The incidence of gastric tuberculosis, therefore, was 0.37 per cent for the entire series of cases and 2 per cent for the cases in which the patients had died of tuberculosis. Simmonds [9] observed 18 instances (0.76 per cent) of gastric tuberculosis in 2,360 cases in which necropsy was performed. In 1929 Good collected a total of 71,871 cases in which the presence or absence of gastric tuberculosis had been recorded by various investigators. The incidence of gastric tuberculosis in this series of cases was 0.34 per cent. This probably is the most accurate figure available as to the incidence of this condition. In 15,165 of the cases in this series the patients had tuberculosis elsewhere in the body; the incidence of tuberculosis, therefore, was 1.4 per cent for the latter group of cases.

The incidence of gastric tuberculosis found at surgical exploration is particularly interesting, since it is at operation rather than at necropsy that the diagnosis should be made. Clairmont [10] reported 2 instances in a series of 258 consecutive gastric operations; Demel [11] found 3 in 1,568 gastric explorations; and Knoflach and Pape [12] found 5 in 4,000 consecutive histologically controlled operations at the University of Vienna. Good reported 3 instances in 7,416 consecutive gastric operations at the Mayo Clinic. The average incidence of gastric tuberculosis found on gastric exploration in cases reported by these investigators is about 0.12 per cent. Gastric tuberculosis is certainly a rare condition, but it does deserve some diagnostic consideration, especially if there is evidence of tuberculosis elsewhere in the body.

MODES OF INFECTION

Practically all writers on the subject of tuberculosis of the stomach agree that there are four possible routes by which infection may occur: (1) through the mucosa (direct infection); (2) through the blood

8. Glaubitt, cited by Broders.[6]

9. Simmonds, M.: Ueber Tuberculose des Magens, München. med. Wchnschr. **47**:317-318 (March) 1900.

10. Clairmont, P.: Bericht über 258 von Prof. v. Eiselsberg ausgegührte Magenoperationen, Arch. f. klin. Chir. **76**:180-322, 1905.

11. Demel, N., cited by Knoflach and Pape.[12]

12. Knoflach, J. G., and Pape, R.: Ein Fall von polypöser, nicht ulcerierter Magentuberkulose, Wien. klin. Wchnschr. **47**:1288-1290 (Oct.) 1934.

stream; (3) through the lymphatic stream, and (4) by continuity and contiguity of structure. That the stomach is highly immune to tuberculosis is beyond question. In this respect it is similar to the thyroid gland, the salivary glands, the esophagus, the pancreas, the gallbladder, the ovaries, the uterus and the heart, which are rarely the sites of tuberculous infection. Unfortunately it is not known at present what factors these organs have in common that make them resistant to tuberculosis.

There has been considerable controversy concerning the usual route of tuberculous infection of the stomach. After a review and consideration of the evidence it must be admitted that infection may occur by any of the four routes and that reasonably authentic instances of infection by each have been described. On the other hand, it must be conceded that the stomach has considerable immunity to infection by the tubercle bacillus by any route. Infection probably never occurs through the intact mucosa; it occurs through erosion, ecchymosis, gastritis, ulcer and carcinoma, which under some conditions can act as portals of entry for the infection. Retrograde lymphatic infection from the mediastinal to the perigastric lymph nodes apparently occurs not infrequently. The most common route of infection is beyond doubt the blood stream. This has been proved by the animal experiments of Arloing and Montemartini [13] and by the bulk of clinical evidence.

The remarkable resistance of the stomach to tuberculous infection, often in the face of constant exposure to active, virulent tubercle bacilli in the sputum or in contaminated food, has been a subject of considerable interest and investigation. It has been variously attributed to the following factors: (1) the effect of the gastric juice on the tubercle bacilli; (2) the scarcity of the lymph follicles and lymphatics in the walls of the stomach; (3) the rapid emptying of the stomach; (4) the integrity of the gastric mucous membrane; and (5) resistance of muscular tissue to tuberculous infection.

Undoubtedly, no one factor is entirely responsible for the immunity of the stomach to tuberculous infection. The gastric juice has been shown by extensive experiments to be an almost negligible factor, because not only is the value for the acidity of the gastric contents usually lowered in cases of tuberculosis, but a normal gastric juice has been shown to have little or no effect on tubercle bacilli unless it is in contact with them for at least twelve hours. The sparsity of lymph follicles is probably of considerable importance, since the tubercle bacillus has a strong predilection for the lymphatic system and naturally would not be common in an organ with a meager lymphatic supply. Furthermore, the fact that the condition occurs most frequently in the pyloric region, where the lymph follicles are abundant, supports this contention. The

13. Montemartini, cited by Rodríguez Olleros and de la Viesca García.[16]

rapid emptying time of the stomach is doubtless a factor of major importance, since it does not allow sufficient contact of the tubercle bacillus and gastric mucosa to permit infection to occur, especially if the gastric mucosa is intact.

PATHOLOGIC CHANGES

Tuberculosis is an infectious disease caused by the tubercle bacillus. The lesion produced is variable, and the changes depend on many factors, such as the number and virulence of the organisms, their dissemination in the body and the resistance of the host. The most characteristic lesion is the tubercle (figs. 1, 2, and 3), but its structure may vary with some of the factors already mentioned. Occasionally

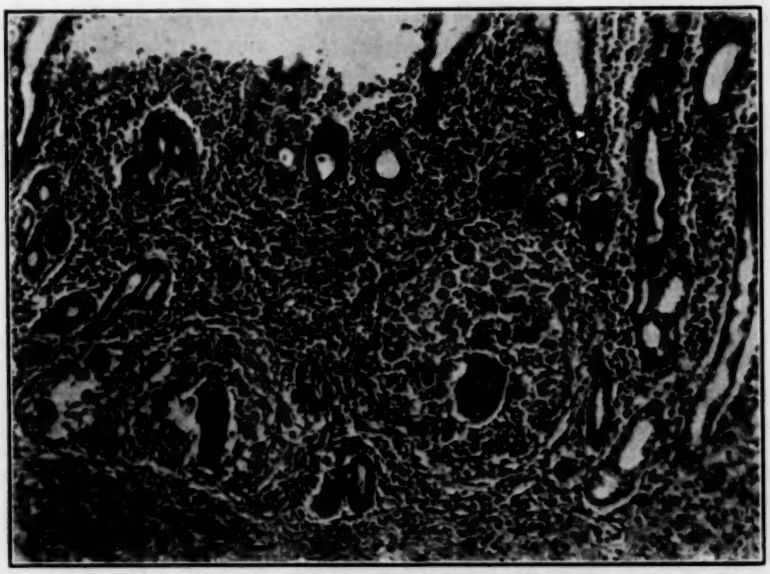

Fig. 1.—Submucous tubercles, epithelioid cells and giant cells; × 90.

the tubercle bacillus may excite a diffuse, acute inflammatory reaction. The effects of infection by the tubercle bacillus may be a result of local destruction of tissue or the products of the tubercle bacillus, or both.

Although many cases of gastric tuberculosis had been reported previously, it was not until 1917, when Broders reviewed and analyzed 305 cases of gastric tuberculosis collected from the literature, that the pathologic criteria for a diagnosis were established. Broders recommended the following criteria for the diagnosis of tuberculosis of the stomach: (1) the diagnosis may be considered positive in all cases in which there is a pathologic picture of tuberculosis of the stomach plus the presence of the bacillus of tuberculosis in the depths of the lesion; (2) the diagnosis may be considered probable in all cases in which there is a

histologic picture of tuberculosis of the stomach, and (3) the diagnosis should be considered possible in all cases in which there is a good description of the gross lesions of tuberculosis of the stomach or a good

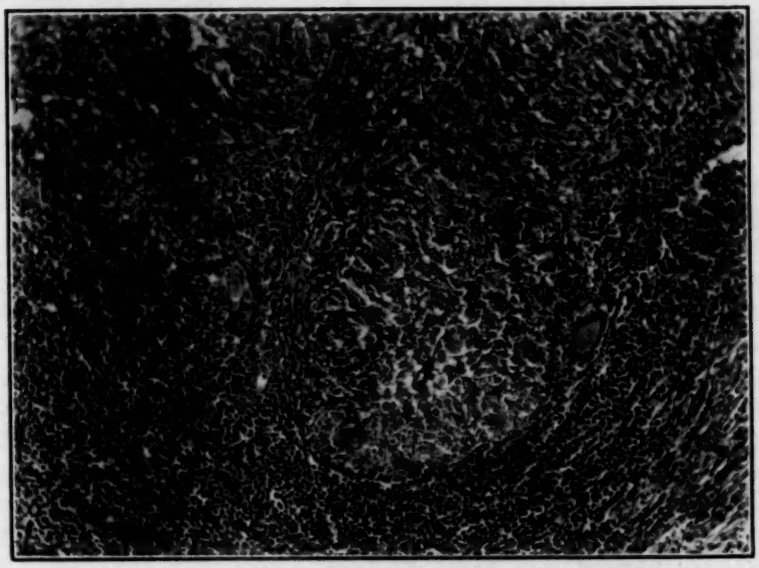

Fig. 2.—Tubercle and giant cells; × 100.

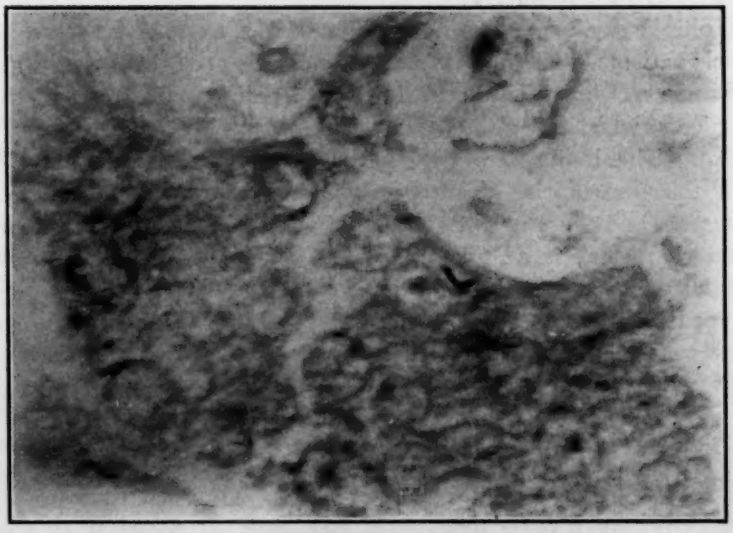

Fig. 3.—Tubercle bacillus in giant cell; × 1060.

description of the gross lesions and a poor description of the histologic lesions. Cases which do not meet these requirements should not be considered proved instances of tuberculosis of the stomach. It is inter-

esting to note that in nearly half of the cases reviewed by Broders the diagnosis was considered questionable or was rejected, whereas this was true in only 2 of the 27 cases which were reported between 1929 and 1936.

The pathologic manifestations of gastric tuberculosis are varied, and their study is interesting because of the wide variety of lesions that have been described. A classification of types is difficult because of the frequency of bizarre lesions which do not fit readily into any group. The classification suggested by Biernath,[14] which is as nearly complete as can be desired, is as follows: (1) simple gastritis in phthisic patients; (2) multiple small erosions and ulcers of the mucosa; (3) an ulcerating type; (4) a hypertrophic, infiltrating form; (5) a sclerosing inflammatory type; (6) acute miliary dissemination, and (7) extragastric forms of tuberculosis which involve the stomach. The first type may result in any of the other types.

There are no extensive figures available which indicate the incidence of simple gastritis among phthisic patients. Marfan[15] reported gastritis in 18 of 27 cases in which necropsy was performed on tuberculous patients. The report of gastroscopic examinations performed on tuberculous patients by Rodríguez Olleros and de la Viesca García[16] likewise indicated that the incidence of gastritis is high. This type of lesion is manifested by a thickening of the gastric mucosa, by hyperemia and microscopically by round cell infiltration of the mucous and submucous layers of the stomach.

Multiple small erosions and ulcers of the mucosa are rare among phthisic patients. The most typical case of this group was that described by Hamilton,[17] in which there were between 115 and 120 small erosions and ulcers which involved a considerable proportion of the gastric mucosa. The lesions are superficial; they penetrate the mucosa but never the muscularis. There is some hypertrophy of the mucous membrane, and there is considerable hyperemia. The histologic picture is that characteristic of tuberculosis, associated with the formation of tubercles and round cell infiltration. There are usually some phlebitis and endarteritis in the region of the tubercles. The perigastric lymph nodes are frequently involved. This involvement is sometimes associated

14. Biernath, P.: Zur Kasuistik der Magentuberkulose, Deutsche med. Wchnschr. **47**:1091-1092 (Sept. 15) 1921.

15. Marfan, B. J. A., cited by Broders.[6]

16. Rodríguez Olleros, A., and de la Viesca García, P.: El estómago tuberculoso y el estómago de los tuberculosos, Rev. españ. de enferm. d. ap. digest. y de la nutrición **1**:745-764 (Oct.) 1935.

17. Hamilton, A.: Multiple Tuberculous Ulcers of the Stomach with a Report of Three Cases, Bull. Johns Hopkins Hosp. **8**:75-79 (Jan.) 1897.

with general miliary tuberculosis, but according to Simmonds it frequently occurs independently of general involvement.

The ulcerating type of gastric tuberculosis is the most frequent and the most important. In the 5 cases observed at the Mayo Clinic the disease was of this type. This type occurs in about 80 per cent of all cases of tuberculosis of the stomach. In Broders' study of 305 cases it was present in 81.6 per cent of all cases in which the diagnosis was positive and in 80.5 per cent of all cases in which the diagnosis was considered probable. The ulceration is usually in the pyloric region and is more frequently on the lesser than on the greater curvature. Good reported 17 pyloric lesions in 26 cases. Ricard and Chevrier reported that in 34.7 per cent of their cases the lesion was situated at the pylorus. The pylorus is often adherent to the head of the pancreas or to the liver, the transverse colon or the duodenum. The occurrence of a gastroduodenal fistula was reported by Mathieu and Rémond.[18] It is generally agreed that the high incidence of tuberculosis in the pyloric region is due largely to the number of lymph follicles in that region as compared to the rest of the stomach. Superimposition of tuberculosis on a nonspecific ulcer (which is common in the pyloric region) may likewise be a factor. Simmonds said that this is the most common origin of tuberculous ulceration.

The ulcer is usually not more than 1 to 2 cm. in diameter. However, it may be 10 by 20 cm. in diameter, which was the size of the ulcer in a case reported by Glaubitt. It is usually shallow and rarely penetrates beyond the submucosa, but instances of perforation have been reported by Kundrat,[19] Marfan, Paulicky,[20] and Struppler.[21] The ulcer is practically identical with that associated with intestinal tuberculosis. The edges are ragged, undermined and overhanging, and the surrounding mucosa is thickened, hyperemic and edematous. The floor of the ulcer is covered with necrotic débris and is usually gray or yellow. There is considerable peritoneal thickening in the vicinity of the ulcer. The regional lymph nodes are often caseous and necrotic.

Microscopically, there are numerous typical epithelioid and giant cell tubercles in the submucosa surrounding the ulcer, and the infection may burrow along the submucosa for a considerable distance in all directions. There is necrosis of the base and hypertrophy of the margins of the

18. Mathieu and Rémond, cited by Broders.[6]

19. Kundrat, cited by Benjamin, J.: Ueber einen Fall von lymphogen entstandenem tuberkulösem Magenschwür, Beitr. z. Klin. d. Tuberk. **84**:249-254, 1933.

20. Paulicky, cited by Abbott, D. P.: Tuberculosis of the Stomach, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1923, vol. 7, pp. 511-516.

21. Struppler, T., cited by Broders.[6]

ulcer. Considerable small round cell infiltration is seen in the surrounding tissues. Endarteritis and phlebitis of regional arteries and veins are common, but the capillaries are usually dilated. There may be some lymphocytic infiltration of the muscular layers, but the infection is chiefly limited to the mucosa and submucosa. The peritoneum is thickened and congested over the ulcer.

The tuberculous granulations around the margins of the ulcer and also the healing of the ulcer may lead in the later stages to scarring and thickening of the pylorus. This transforms the ulcer into a hard cartilage-like mass which causes contraction of the pyloric ring and obstruction to the passage of gastric contents into the duodenum. Pyloric stenosis may also be produced by spasm, by perigastric adhesions or by compression of the pylorus by enlarged and caseous regional lymph nodes.

The hypertrophic infiltrating type is the second most common type of gastric tuberculosis. It usually involves chiefly the pyloric region and forms a firm, indurated mass which grossly resembles the scirrhous type of carcinoma of the stomach. In this condition the formative process is in excess of the destructive processes, and there is a great formation of tuberculous granulation tissue; the mucous membrane is folded, thickened and nodular, and it may encroach on the lumen of the pyloric region so much as to cause almost complete obstruction. Giant cells are abundant, but miliary tubercles are not common, and caseation is absent. Considerable edema and small cell infiltration of the mucosa and submucosa are present. Endarteritis and phlebitis are common. The diagnosis may be difficult unless there is involvement of regional lymph nodes. Tumor masses the size of walnuts have been described by Melchior [22] and Konjetzny.[23] Beresgonowski,[24] Pfanner,[25] and von Tappeiner [26] have described lesions the size of eggs, and in Ruge's [27] case the mass was the size of a human fist.

Acute miliary tuberculosis of the stomach is relatively common; it usually is associated with general miliary tuberculosis. This lesion is

22. Melchior, E.: Tuberculosis of the Stomach, abstracted, J. A. M. A. **87**: 888 (Sept. 11) 1926.

23. Konjetzny, cited by Pohl, R.: Ueber Tuberkulose des Magens, Röntgenpraxis **4**:423-428 (May) 1932.

24. Beresgonowski, cited by Pohl, R.: Ueber Tuberkulose des Magens, Röntgenpraxis **4**:423-428 (May) 1932.

25. Pfanner, cited by Pohl, R.: Ueber Tuberkulose des Magens, Röntgenpraxis **4**:423-428 (May) 1932.

26. von Tappeiner, H.: Beitrag zur Kenntnis der tuberkulösen Pylorusstenose, Beitr. z. klin. Chir. **66**:371-376 (March) 1910.

27. Ruge, cited by Pohl, R.: Ueber Tuberkulose des Magens, Röntgenpraxis **4**:423-428 (May) 1932.

caused by tubercle bacilli which are poured into the blood stream from some focus of infection and which are distributed throughout the body. Miliary tuberculosis of the stomach is not of any clinical importance, since it is usually only a small factor in a rapidly fatal condition. Wilms [28] has reported an interesting case of this type, in which the patient was a child aged 9 months.

Extragastric forms of tuberculosis which involve the stomach occur when tuberculosis invades the stomach from neighboring organs, such as the duodenum and the pancreas or the perigastric lymph nodes.

Nedelec [29] called attention to a rare type of gastric tuberculosis in which "cold abscesses" of the stomach were found in the cases reported by Schlesinger [30] in 1914 and by Mathieu and Rémond [31] in 1921. A solitary tubercle of the stomach is extremely rare. Van Wart [32] has described an interesting case in which the tubercle was 3.5 cm. in diameter. It was situated on the greater curvature, 6 cm. from the cardia. Tuberculosis was not demonstrable elsewhere in the body; hence there was no definite evidence that this lesion was not primary in the stomach. Genkin and Sosnowik [33] in 1934 reported a case in which there were many fistulas which ended blindly in the thick wall of a tuberculous stomach. These authors called particular attention to the thrombosis of the blood vessels around the fistulas. The route of infection in this case was apparently by retrograde lymphatic spread from tuberculous hilar nodes to the perigastric lymph nodes.

In brief, tuberculosis of the stomach may appear in any stage from acute fulminating to chronic infiltrating forms, and the diagnosis must usually be made by histologic examination.

RELATION OF GASTRIC CARCINOMA AND TUBERCULOSIS

The association of carcinoma and tuberculosis in the same body or organ has been a subject of considerable interest and controversy among pathologists for many years, and extensive literature has accumulated regarding this subject. At present the weight of evidence, as voiced by

28. Wilms, M.: Miliartuberkulose des Magens, Centralbl. f. allg. Path. u. path. Anat. **8**:783-789 (Sept.) 1897.

29. Nedelec, M.: La tuberculose de l'estomac, Arch. franco-belges de chir. **34**:76-104 (Feb.) 1934.

30. Schlesinger, H., cited by Knoflach and Pape.[12]

31. Mathieu and Rémond, cited by Abbott, D. P.: Tuberculosis of the Stomach, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1923, vol. 7, pp. 511-516.

32. Van Wart, R. M.: Solitary Tubercle of the Stomach, Bull. Johns Hopkins Hosp. **14**:235-237 (Sept.) 1903.

33. Genkin, S., and Sosnowik, J.: Klinik und Pathologie einiger Formen der Magen- und Lebertuberkulose, Virchows Arch. f. path. Anat. **292**:315-321 (April) 1934.

Menniti,[34] Schacter,[35] Broders,[36] and Cooper,[37] supports the contention that tuberculosis and carcinoma in the same body or organ are not antagonistic. This contention certainly is borne out in the case of tuberculosis and carcinoma of the stomach. To date a total of 368 cases of gastric tuberculosis have been reported in the literature, and of these not more than 60 per cent can be classed as positive or probable cases of gastric tuberculosis according to the criteria postulated by Broders. An analysis of these same cases revealed that in 30 of the 368 cases gastric tuberculosis and gastric carcinoma were coexistent. This incidence of association is rather high, certainly higher than occurs in most organs of the body in which these conditions can coexist. Perhaps this can be accepted as evidence in support of the theory that cancer, ulcer and erosion of the gastric mucosa may lower its resistance to tuberculous infection and act as portals of entry for infection. Certainly, this incidence of associated lesions seems too high to be explained entirely by coincidence.

The first case of associated gastric tuberculosis and carcinoma was reported by Clement[38] in 1895. Since then, 28 additional cases of coexisting gastric tuberculosis and carcinoma and 1 case of associated sarcoma and tuberculosis have been reported. In 5 cases the carcinoma was considered primary; in 3 cases tuberculosis was believed to have developed first. No opinion was stated in the other cases. In 12 cases there was definite evidence of pulmonary tuberculosis.

These cases of associated gastric tuberculosis and carcinoma are interesting chiefly as pathologic curiosities. It is generally agreed that there is nothing about the history or clinical findings that is of any particular value as regards the diagnosis, and the treatment is always surgical.

DIAGNOSIS

At the outset it must be said that there is no way in which a definite clinical diagnosis of tuberculosis of the stomach can be made. There are no characteristic signs or symptoms, and there is no laboratory test or group of tests that can indicate to the observer the nature of the disease. The difficulty lies largely in the fact that the symptoms and signs resemble, or are identical with, those of pathologic gastric condi-

34. Menniti, M.: Sull'associszione di tuberculosi e neoplasie maligne, Pathologica **25**:180-190 (March 15) 1933.

35. Schacter, cited by Cooper.[37]

36. Broders, A. C.: Tuberculosis Associated with Malignant Neoplasia: Report of Twenty Cases, J. A. M. A. **72**:390-394 (Feb. 8) 1919.

37. Cooper, F. G.: The Association of Tuberculosis and Carcinoma, Am. Rev. Tuberc. **25**:108-147 (Jan.) 1932.

38. Clement, G.: Ueber seltnere Arten der Combination von Krebs und Tuberculose, Virchows Arch. f. path. Anat. **139**:35-58, 1895.

tions infinitely more common than gastric tuberculosis. Gastric tuberculosis closely resembles gastric ulcer, gastric carcinoma and gastric syphilis and must sometimes be distinguished from tumor of the pancreas, carcinoma of the gallbladder, benign tumor of the stomach, pylorospasm and hypertrophic pyloric stenosis. The problem is further complicated by the fact that patients frequently may have two or more of these conditions in the stomach at the same time. It is true of tuberculosis of the stomach, as of most rare diseases, that the diagnosis is not made because the condition is not thought of, and the rarity of the condition makes this only natural. However, the disease has been diagnosed clinically in 6 instances, by von Schlesinger, Haudek,[39] Spengler,[40] Pohl,[41] Lapeyre,[42] and Pop and Hanganutiu,[43] and it is one of the purposes of this paper to call the attention of clinicians to this condition so that it may be considered more frequently in the differential diagnosis of gastric disease.

Gastric tuberculosis usually affects young adults; it rarely affects persons beyond 35 years of age, but in some cases which have been reported the patients were adults who were 60 and 70 years of age, and in others they were children who were less than a year old. It occurs among male patients approximately twice as frequently as among female patients. The onset is usually insidious, but the course is steadily progressive. The symptoms most frequently noted are loss of appetite and a sense of epigastric fulness and pressure after meals, especially if solid food has been eaten. There may be a burning, gnawing pain which comes on two or more hours after meals and is relieved by the ingestion of food. As the condition progresses, vomiting develops, and there is pain in the upper part of the abdomen, which often is cramplike. This pain is usually relieved by vomiting. As the vomiting grows progressively worse the vomitus becomes stagnant and frequently contains food which was eaten several meals previously. The patient gradually loses strength and weight. Occasionally, hematemesis occurs. Arloing noted hematemesis in 9 of the 147 cases he reported. Benjamin [44] reported that

39. Haudek, cited by Knoflach and Pape.[12]

40. Spengler, cited by Knoflach and Pape.[12]

41. Pohl, R.: Ueber Tuberkulose des Magens, Röntgenpraxis **4**:423-428 (May) 1932.

42. Lapeyre, L. N.: Ulcère tuberculeux de l'estomac: Une observation complète: clinique, anatomique, histologique, Gaz. méd. de France (supp. Gastroenterol.), March 1, 1933, pp. 3-6.

43. Pop, A., and Hanganutiu, M.: Klinische und röntgenologische Betrachtungen über die Tuberkulose des Magens, Zentralbl. f. Chir. **59**:1629-1635 (July) 1932.

44. Benjamin, J.: Ueber einen Fall von lymphogen entstandenem tuberkulösem Magengeschwür (Tödliche Hämatemesis), Beitr. z. Klin. d. Tuberk. **84**: 249-254, 1933.

fatal hematemesis occurred in the cases reported by Bignon,[45] Kundrate, Brechemin,[46] Long,[47] Plate,[48] and Reinhold,[49] and in 1 case of his own. Diarrhea, which appears early and continues throughout the course of the disease, is rather characteristic, but constipation occurs not infrequently, as has been pointed out by Curschmann.[50] A history of pulmonary tuberculosis may be entirely lacking.

Physical examination usually reveals that the patient is pale and thin and appears ill. There may or may not be evidence of pulmonary tuberculosis. The stomach is often dilated, and occasionally its outline can be made out without difficulty. Visible peristalsis is common, and it may be possible to elicit a succussion splash. There is usually considerable epigastric tenderness, and in 50 per cent of cases there is a palpable mass in the pyloric region. Usually the mass is firm, well defined and movable. A daily variation of temperature is highly suggestive of tuberculosis.

As mentioned previously, laboratory data do not offer anything pathognomonic of gastric tuberculosis. There is usually some anemia, and this may be striking, but diagnostically it cannot be relied on. Analysis of the gastric contents is not conclusive but does offer some information. As has been shown by Cohen [51] and others, the acidity of the gastric contents in persons with tuberculosis of the stomach is much lower than it is among normal healthy persons. In the large majority of cases of gastric tuberculosis the acidity of the gastric contents is decreased, and complete anacidity is not uncommon, as it occurred in the cases reported by Alessandri,[52] Alexander,[53] Fujii [54] and others. In Lee's [55] case no free hydrochloric acid was observed even after injection of histamine, which usually has the property of stimulating the secretion of acid. On the other hand, in cases which were reported by Curschmann and Schlesinger there was hyperchlorhydria. There may be occult

45. Bignon, cited by Benjamin.[44]

46. Brechemin, G., cited by Lusena, G.: Stenosi piloriea da granuloma tubercolare, Arch. ital. di chir. **4**:1-31, 1921.

47. Long, cited by Benjamin.[44]

48. Plate, cited by Benjamin.[44]

49. Reinhold, H., cited by Benjamin.[44]

50. Curschmann, H.: Klinischer Beitrag zur Tuberkulose des Pylorus, Beitr. z. Klin. d. Tuberk. **2**:127-140 (June) 1904.

51. Cohen, S. J.: Study of Gastric Function in Pulmonary Tuberculosis, Nat. Tuberc. A. Tr. **28**:184-186 (June) 1932.

52. Alessandri, cited by Broders.[6]

53. Alexander, M.: Beitrag zur Tuberkulose des Magens, Deutsches Arch. f. klin. Med. **86**:212-216 (Dec.) 1906.

54. Fujii, R., in Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie für Studierende und Ärzte, Berlin, W. de Gruyter & Co., 1922, vol. 1, pp. 528-529.

55. Lee, F. C.: The Surgery of Tuberculosis of the Pylorus, Am. Rev. Tuberc. **26**:323-368 (Oct.) 1932.

blood in the gastric contents, but the finding of tubercle bacilli in the secretions may be of slight significance. Examination of the stools rarely gives much information. Even the finding of occult blood in the stools is of little significance, as it may be due to the hemophthisis of pulmonary tuberculosis or to any number of other gastrointestinal conditions. The urine is practically always normal. The injection of tuberculin has been advocated by some as a diagnostic method. It cannot be used as a routine test, because of the danger of a severe reaction or even of perforation. This test is mentioned only to be condemned.

Roentgenologic investigations are of considerable value in determining the presence or absence of a gastric lesion, but they rarely contribute much of a definitely diagnostic nature, since the roentgenogram of the lesion is almost identical with that produced by more common gastric lesions, such as carcinoma and ulcer. Roentgenologists of great experience can frequently differentiate between a carcinomatous lesion and a granulomatous lesion such as occurs with tuberculosis or syphilis, but there are no definite criteria for the differentiation of these two lesions. With the ulcerating type of gastric tuberculosis, which makes up 80 per cent of the lesions, the roentgenologic picture is that of a nonspecific gastric ulcer, with perhaps a little more scarring and contracture than occur with the ordinary ulcer. The hypertrophic, infiltrating type produces nonspecific pyloric stenosis, which simulates that produced by either carcinoma or syphilis of the stomach. Renander [56] has described a cufflike infiltration with equal contours and a uniform circular shadow as being characteristic of gastric tuberculosis. Rother [57] noticed a slight break between the bulb and the canal and believed this finding was of considerable significance. Haudek has called attention to the uniform narrowing of the pylorus. Schmitz [58] has postulated that if infiltration extends into the duodenum one should suspect tuberculosis, as carcinoma never extends into the duodenum. Pop and Hanganutiu were impressed by the smooth, amputated appearance of the pylorus in a case of tuberculosis of the stomach observed by them, as compared with the irregular outline common in cases of carcinoma of the stomach. There is usually some evidence of pulmonary tuberculosis, and it should always be searched for. Leriche [59] found roentgenologic evidence of pulmonary tuberculosis in all but 2 of a series of 24 cases of tuberculous gastric ulcers. Roentgenologic evidence of osseous or intestinal tuberculosis would be suggestive. Roentgenologists are agreed that it is impossible to make a diagnosis of gastric tuberculosis from the roentgenologic appearance at a single examination.

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56. Renander, A.: Einige röntgenologisch Beobachtete Fälle von Magentuberkulose, Acta radiol. **11**:636-648, 1930.

57. Rother, cited by Renander.[56]

58. Schmitz, cited by Pop and Hanganutiu.[43]

59. Leriche, R., cited by Pohl.[41]

Lee's dictum that when the patient is an adult 20 to 40 years of age with signs of pyloric obstruction, diarrhea, fever, a movable pyloric mass and pulmonary tuberculosis, one should suspect gastric tuberculosis, holds good for a majority of cases, but it should be extended to include any person who has a digestive disturbance and evidence of tuberculosis anywhere in the body.

PROGNOSIS

In considering the prognosis of gastric tuberculosis one cannot regard the disease as a clinical and pathologic entity confined to the stomach. Gastric tuberculosis is a complication of an infectious process with foci elsewhere in the body. It is doubtful if a case of proved primary gastric tuberculosis has ever been reported, although a number of cases have been reported as such. According to the statistics of Glaubitt and Blas,[60] tuberculosis of the stomach is associated with pulmonary tuberculosis in 94 to 100 per cent of cases, with intestinal tuberculosis in 69 to 91.5 per cent and with tuberculosis of the liver and the lymph nodes in 74 and 68.1 per cent, respectively.

The only satisfactory treatment of tuberculosis depends on rest, fresh air, sunshine and adequate nutrition. Interference with or lack of any of these elements is immediately harmful. Gastric tuberculosis occurs only as a complication of an already existing tuberculous process, and striking as it does at one of the keystones of tuberculosis therapy, adequate nutrition, it rapidly endangers the life of the afflicted person. The loss of appetite, digestive disturbance, vomiting and diarrhea so often produced by gastric tuberculosis result in a loss of strength and weight and a degree of dehydration that are extremely dangerous to the patient already weakened by tuberculosis. Return of normal gastric function must be brought about promptly or the lowered resistance of the patient will permit an extension of the primary tuberculous focus, which may be fatal. Restoration of gastric function can be brought about only by surgical methods. If possible, the infected portion of the stomach should be removed. If this is not possible, continuity of the gastrointestinal tract must be restored by means of a gastroenterostomy, which allows nutrition to be maintained with as little interference as possible. Gastric operations in cases of tuberculosis are extremely difficult and dangerous. The frequent coexistence of a tuberculous process involving the transverse colon, the duodenum, the liver, the pancreas and the regional lymph nodes further complicates this perplexing surgical problem. The possible development of tuberculous bronchopneumonia as a result of the anesthesia or of shock incident to the operation constitutes a considerable hazard. Even so, the prognosis is infinitely better with operation than without.

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60. Blas, M., cited by Lee.[58]

TREATMENT

The treatment of gastric tuberculosis still leaves much to be desired, although with improvements in diagnostic methods patients are seeking treatment before the tuberculous process has extended too far for satisfactory treatment. It must be admitted that too few patients who have gastric tuberculosis are given the benefit of a correct clinical diagnosis. However, medical treatment has little to offer, and surgical treatment must always depend on what is found at exploration; therefore, the patient has little to lose if a diagnosis of a surgical gastric lesion is made and prompt surgical attack is carried out. Good's dictum that surgical treatment be prescribed for almost all chronic gastric lesions does not seem too radical.

In all cases of gastric tuberculosis reported up to 1889 the lesions were observed at necropsy. In that year Ricard and Chevrier performed the first surgical operation in a case of gastric tuberculosis. An anterior gastroenterostomy was performed. This case stimulated Ricard and Chevrier to review the literature on gastric tuberculosis, and in their report they reached the following conclusion in regard to treatment: "The knowledge of the pathologic anatomy of the causal lesions imposes the abandonment of certain varieties of intervention. Resection is useless because impossible, and if attempted would be dangerous." Gastroenterostomy was generally accepted as the treatment of choice until 1902, when Koerte [61] performed the first resection of the stomach for gastric tuberculosis. A Billroth II type of resection was done.

The surgical procedure carried out should usually be dictated by the findings on exploration. Gastric resection is the treatment of choice whenever possible, and gastroenterosotomy should be used only when the patient is in bad condition or when resection is contraindicated by extensive involvement of other abdominal viscera, generalized peritoneal involvement or severe intestinal tuberculosis. Knoflach and Pape collected 58 cases in which resection was performed. Good results were obtained in 36 of these cases. Lee collected 80 cases in which gastric tuberculosis involved the pylorus. In 51 cases gastroenterostomy was performed, and in 19 resection was the procedure carried out. Forty-five per cent of the patients who were subjected to gastroenterostomy were well after the operation. Sixty-five per cent of the patients who underwent gastrectomy were well after the operation. In all 5 cases observed at the clinic the patients have been treated by resection.

After all, the type of operation preferable is not a matter which merits too much consideration, as the operation must depend on the pathologic process present and on its extent. In general, resection should be performed for any chronic, well localized type of gastric tuberculosis

61. Koerte, cited by Nedelec.[29]

in which there is not a generalized involvement of the abdominal cavity or viscera, extensive pulmonary tuberculosis or a general physical condition contraindicating a prolonged operative procedure. Gastroenterostomy usually should be performed whenever resection is not justified. Other types of surgical procedure, such as pyloroplasty and gastroduodenostomy, are rarely indicated.

SUMMARY

Tuberculosis of the stomach is a comparatively rare gastric lesion. Only 368 cases have been reported in the literature. The disease may occur at any age but is most common in persons of 35 to 45 years. Males are affected twice as frequently as are females. Infection of the stomach usually occurs by way of the blood stream but may occur by way of the lymphatics, by direct infection of the mucosa and by direct continuity or contiguity of structure. There is no completely satisfactory explanation of the relatively high immunity of the stomach to tuberculosis. The chief pathologic types of gastric tuberculosis are: (1) the ulcerating type; (2) the hypertrophic infiltrating type; (3) acute miliary dissemination; and (4) extragastric forms involving the stomach. The ulcerating type is present in at least 80 per cent of cases. In approximately 10 per cent of cases of gastric tuberculosis the disease is associated with carcinoma. There is no proof of antagonism between carcinoma and tuberculosis. The coexistence of the two conditions in the stomach seems too high to be entirely coincidental, but no reasonable explanation for this association has been suggested. Clinically, tuberculosis of the stomach closely simulates peptic ulcer, gastric carcinoma and gastric syphilis. Only rarely can the diagnosis be made before histologic examination of the gastric lesion. A positive diagnosis of gastric tuberculosis can be made only by the demonstration of the tubercle bacillus in the lesions. The treatment of gastric tuberculosis should always be surgical. Resection of the involved portion of the stomach is the operation of choice whenever possible.